

METHODS FOR IDENTIFYING RISK OF OSTEOARTHRITIS AND TREATMENTS THEREOF

Field of the Invention

[0001] The invention relates to genetic methods for identifying risk of osteoarthritis and treatments that specifically target such diseases.

Background

[0002] Osteoarthritis (OA) is a chronic disease usually affecting weight-bearing synovial joints. There are approximately 20 million Americans affected by OA and it is the leading cause of disability in the United States. In addition to extensive human suffering, OA also accounts for nearly all knee replacements and more than half of all hip replacements in the United States. Despite its prevalence, OA is poorly understood and there are few treatments available besides anti-inflammatory drugs and joint replacement.

[0003] Osteoarthritis (OA) is a disease caused by degeneration of articular cartilage and subsequent joint deformation. In addition to risk factors like body weight, joint injury and age, there is a strong hereditary component to OA, reflected by high heritability estimates from twin studies. So far, few of the genes responsible for this genetic component have been identified.

Summary

[0004] It has been discovered that certain polymorphic variations in human genomic DNA are associated with osteoarthritis. In particular, polymorphic variants in loci containing *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXLI*, *CASPR4* and *APOL3* regions and other regions in Table B of human genomic DNA have been associated with risk of osteoarthritis.

[0005] Thus, featured herein are methods for identifying a subject at risk of osteoarthritis and/or a risk of osteoarthritis in a subject, which comprise detecting the presence or absence of one or more polymorphic variations associated with osteoarthritis in or around the loci described herein in a human nucleic acid sample. In an embodiment, two or more polymorphic variations are detected in two or more regions of which one is the *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXLI*, *CASPR4* or *APOL3* region or other region in Table B. In certain embodiments, 3 or more, or 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 or more polymorphic variants are detected.

[0006] Also featured are nucleic acids that include one or more polymorphic variations associated with occurrence of osteoarthritis, as well as polypeptides encoded by these nucleic acids. In addition, provided are methods for identifying candidate therapeutic molecules for treating osteoarthritis, as well as methods for treating osteoarthritis in a subject by identifying a subject at risk of osteoarthritis and treating the subject with a suitable prophylactic, treatment or therapeutic molecule.

[0007] Also provided are compositions comprising a cell from a subject having osteoarthritis or at risk of osteoarthritis and/or a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleic acid referenced in Table B, with a RNAi, siRNA, antisense DNA or RNA, or ribozyme nucleic acid designed from a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B. In an embodiment, the RNAi, siRNA, antisense DNA or RNA, or ribozyme nucleic acid is designed from a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B that includes one or more polymorphic variations associated with osteoarthritis, and in some instances, specifically interacts with such a nucleotide sequence. Further, provided are arrays of nucleic acids bound to a solid surface, in which one or more nucleic acid molecules of the array have a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B, or a fragment or substantially identical nucleic acid thereof, or a complementary nucleic acid of the foregoing. Featured also are compositions comprising a cell from a subject having osteoarthritis or at risk of osteoarthritis and/or a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* polypeptide or other polypeptide referenced in Table B, with an antibody that specifically binds to the polypeptide. In an embodiment, the antibody specifically binds to an epitope in the polypeptide that includes a non-synonymous amino acid modification associated with osteoarthritis (e.g., results in an amino acid substitution in the encoded polypeptide associated with osteoarthritis). In certain embodiments, the antibody selectively binds to an epitope in the *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* polypeptide, or other polypeptide referenced in Table B, having an amino acid associated with osteoarthritis. Thus, featured is an antibody that binds an epitope having an amino acid encoded by rs1367117, rs1041973 and/or rs398829, such as a isoleucine or threonine encoded by rs1367117 (e.g., a threonine at position 98 in an *APOB* polypeptide), a glutamic acid or alanine encoded by rs1041973 (e.g., an alanine at position 78 in a *IL1RL1* polypeptide), a valine or isoleucine encoded by rs398829 (e.g., a valine at position 245 in a *ADAMTS2* polypeptide), at the corresponding position in the polypeptide.

Brief Description of the Drawings

[0008] Figures 1A-1J show proximal SNPs in a 100-kb window in *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* and *APOL3* regions of genomic DNA, respectively, that were compared between pools of cases and controls. The x-axis corresponds to their chromosomal position and the y-axis to the test P-values (shown on the $-\log_{10}$ scale). The continuous bold line presents the results of a goodness-of-fit test for an excess of significance (compared to 0.05) in a 10 kb sliding window assessed at 1 kb increments.

Detailed Description

[0009] It has been discovered that polymorphic variants in a locus containing a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* region are associated with occurrence of osteoarthritis in subjects. Thus, detecting genetic determinants associated with an increased risk of osteoarthritis occurrence can lead to early identification of a predisposition to osteoarthritis and early prescription of preventative measures. Also, associating a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* polymorphic variant and other variants referenced in Table B with osteoarthritis has provided new targets for screening molecules useful in treatments of osteoarthritis.

Osteoarthritis and Sample Selection

[0010] Osteoarthritis (OA), or degenerative joint disease, is one of the oldest and most common types of arthritis. It is characterized by the breakdown of the joint's cartilage. Cartilage is the part of the joint that cushions the ends of bones, and its breakdown causes bones to rub against each other, causing pain and loss of movement. Type II collagen is the main component of cartilage, comprising 15-25% of the wet weight, approximately half the dry weight, and representing 90-95% of the total collagen content in the tissue. It forms fibrils that endow cartilage with tensile strength (Mayne, R. Arthritis Rheum. 32:241-246 (1989)).

[0011] Most commonly affecting middle-aged and older people, OA can range from very mild to very severe. It affects hands and weight-bearing joints such as knees, hips, feet and the back. Knee OA can be as disabling as any cardiovascular disease except stroke.

[0012] Osteoarthritis affects an estimated 20.7 million Americans, mostly after age 45, with women more commonly affected than men. Physicians make a diagnosis of OA based on a physical exam and history of symptoms. X-rays are used to confirm diagnosis. Most people over 60 reflect the disease on X-ray, and about one-third have actual symptoms.

[0013] There are many factors that can cause OA. Obesity may lead to osteoarthritis of the knees. In addition, people with joint injuries due to sports, work-related activity or accidents may be at increased risk of developing OA.

[0014] Genetics has a role in the development of OA too. Some people may be born with defective cartilage or with slight defects in the way that joints fit together. As a person ages, these defects may cause early cartilage breakdown in the joint or the inability to repair damaged or deteriorated cartilage in the joint.

[0015] Inclusion or exclusion of samples for an osteoarthritis pool may be based upon the following criteria: ethnicity (e.g., samples derived from an individual characterized as Caucasian); parental ethnicity (e.g., samples derived from an individual of British paternal and maternal descent); relevant phenotype information for the individual (e.g., case samples derived from individuals diagnosed with specific knee, hand or hip osteoarthritis (OA); case samples recruited from an OA knee replacement clinic). Control samples may be selected based on relevant phenotype information for the

individual (*e.g.*, derived from individuals free of OA at several sites (knee, hand, hip etc)); and no family history of OA and/or rheumatoid arthritis. Additional phenotype information collected for both cases and controls may include age of the individual, gender, family history of OA, diagnosis with osteoarthritis (joint location of OA (*e.g.*, knee, hips, hands and spine), date of primary diagnosis, age of individual as of primary diagnosis), knee history (current symptoms, any major knee injury, menisectomy, knee replacement surgery, age of surgery), HRT history, osteoporosis diagnosis.

[0016] Based in part upon selection criteria set forth above, individuals having osteoarthritis can be selected for genetic studies. Also, individuals having no history of osteoarthritis often are selected for genetic studies, as described hereafter.

Polymorphic Variants Associated with Osteoarthritis

[0017] A genetic analysis provided herein linked osteoarthritis with polymorphic variant nucleic acid sequences in the human genome. As used herein, the term “polymorphic site” refers to a region in a nucleic acid at which two or more alternative nucleotide sequences are observed in a significant number of nucleic acid samples from a population of individuals. A polymorphic site may be a nucleotide sequence of two or more nucleotides, an inserted nucleotide or nucleotide sequence, a deleted nucleotide or nucleotide sequence, or a microsatellite, for example. A polymorphic site that is two or more nucleotides in length may be 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or more, 20 or more, 30 or more, 50 or more, 75 or more, 100 or more, 500 or more, or about 1000 nucleotides in length, where all or some of the nucleotide sequences differ within the region. A polymorphic site is often one nucleotide in length, which is referred to herein as a “single nucleotide polymorphism” or a “SNP.”

[0018] Where there are two, three, or four alternative nucleotide sequences at a polymorphic site, each nucleotide sequence is referred to as a “polymorphic variant” or “nucleic acid variant.” Where two polymorphic variants exist, for example, the polymorphic variant represented in a minority of samples from a population is sometimes referred to as a “minor allele” and the polymorphic variant that is more prevalently represented is sometimes referred to as a “major allele.” Many organisms possess a copy of each chromosome (*e.g.*, humans), and those individuals who possess two major alleles or two minor alleles are often referred to as being “homozygous” with respect to the polymorphism, and those individuals who possess one major allele and one minor allele are normally referred to as being “heterozygous” with respect to the polymorphism. Individuals who are homozygous with respect to one allele are sometimes predisposed to a different phenotype as compared to individuals who are heterozygous or homozygous with respect to another allele.

[0019] In genetic analysis that associate polymorphic variants with osteoarthritis, samples from individuals having osteoarthritis and individuals not having osteoarthritis often are allelotyped and/or genotyped. The term “allelotype” as used herein refers to a process for determining the allele frequency for a polymorphic variant in pooled DNA samples from cases and controls. By pooling DNA from each group, an allele frequency for each SNP in each group is calculated. These allele frequencies are then compared to one another. The term “genotyped” as used herein refers to a process for determining a

genotype of one or more individuals, where a “genotype” is a representation of one or more polymorphic variants in a population.

[0020] A genotype or polymorphic variant may be expressed in terms of a “haplotype,” which as used herein refers to two or more polymorphic variants occurring within genomic DNA in a group of individuals within a population. For example, two SNPs may exist within a gene where each SNP position includes a cytosine variation and an adenine variation. Certain individuals in a population may carry one allele (heterozygous) or two alleles (homozygous) having the gene with a cytosine at each SNP position. As the two cytosines corresponding to each SNP in the gene travel together on one or both alleles in these individuals, the individuals can be characterized as having a cytosine/cytosine haplotype with respect to the two SNPs in the gene.

[0021] As used herein, the term “phenotype” refers to a trait which can be compared between individuals, such as presence or absence of a condition, a visually observable difference in appearance between individuals, metabolic variations, physiological variations, variations in the function of biological molecules, and the like. An example of a phenotype is occurrence of osteoarthritis.

[0022] Researchers sometimes report a polymorphic variant in a database without determining whether the variant is represented in a significant fraction of a population. Because a subset of these reported polymorphic variants are not represented in a statistically significant portion of the population, some of them are sequencing errors and/or not biologically relevant. Thus, it is often not known whether a reported polymorphic variant is statistically significant or biologically relevant until the presence of the variant is detected in a population of individuals and the frequency of the variant is determined. Methods for detecting a polymorphic variant in a population are described herein, specifically in Example 2. A polymorphic variant is statistically significant and often biologically relevant if it is represented in 5% or more of a population, sometimes 10% or more, 15% or more, or 20% or more of a population, and often 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, or 50% or more of a population.

[0023] A polymorphic variant may be detected on either or both strands of a double-stranded nucleic acid. Also, a polymorphic variant may be located within an intron or exon of a gene or within a portion of a regulatory region such as a promoter, a 5′ untranslated region (UTR), a 3′ UTR, and in DNA (*e.g.*, genomic DNA (gDNA) and complementary DNA (cDNA)), RNA (*e.g.*, mRNA, tRNA, and rRNA), or a polypeptide. Polymorphic variations may or may not result in detectable differences in gene expression, polypeptide structure, or polypeptide function.

[0024] It was determined that polymorphic variations associated with an increased risk of osteoarthritis existed in SEQ ID NO: 1-13 or a nucleotide sequence referenced in Table B. In certain embodiments, polymorphic variants at positions rs910223, rs1367117, rs1024791, rs1041973, rs1465621, rs398829, rs1018810, rs1484086, rs242392, rs8818, rs1395486, rs512294 and/or rs132659 in the human genome were associated with an increased risk of osteoarthritis, and in specific embodiments, the corresponding allele in the right-most column in Table B for each position is associated with an increased risk of osteoarthritis. In other embodiments polymorphic variants at

positions rs1367117, rs1041973 and rs398829 were associated with an increased risk of osteoarthritis, and in specific embodiments, a threonine encoded by rs1367117, an alanine encoded by rs1041973, and a valine encoded by rs398829 were associated with an increased risk of osteoarthritis.

[0025] Polymorphic variants in and around the *APOB* locus were tested for association with osteoarthritis. These include polymorphic variants at positions in SEQ ID NO: 2 selected from the group consisting of 238, 294, 295, 347, 1425, 4891, 5087, 7041, 7121, 7219, 7443, 7485, 10939, 11367, 11571, 11839, 12551, 12646, 13469, 14913, 15205, 15246, 15695, 17473, 17610, 17828, 18130, 18281, 18623, 18890, 21561, 23100, 23872, 24581, 24582, 24983, 27540, 30846, 31415, 31453, 31899, 37000, 38681, 39287, 42951, 45648, 46222, 46687, 47020, 47593, 48513, 49723, 49986, 53018, 53296, 53547, 53899, 53916, 53933, 54305, 55327, 55895, 56143, 56640, 58486, 59576, 63048, 64008, 64018, 64859, 65995, 66905, 67183, 67942, 68101, 68521, 68664, 68988, 69178, 72143, 74183, 74312, 74407, 75518, 76153, 77398, 77615, 79092, 80000, 80125, 80595, 81061, 81151, 81918, 83072, 83137, 83235, 83263, 83279, 83280, 83533, 86856, 87186, 87189, 87727, 87978, 89129, 89556, 89702, 90233, 93060, 94779, 95367, 95844, 95942, 96884, 96938, 97627, 97777, 97871, 98746 and 99663. Polymorphic variants at the following positions in SEQ ID NO: 2 in particular were associated with an increased risk of osteoarthritis: 7219, 7485, 11839, 31899, 37000, 48513, 49986, 56640, 74407, 77398, 93060 and 97627. In particular, the following polymorphic variants in SEQ ID NO: 2 were associated with risk of osteoarthritis: an adenine at position 7219, a guanine at position 7485, an adenine at position 11839, a thymine at position 31899, an adenine at position 37000, a cytosine at position 48513, a guanine at position 49986, a guanine at position 56640, a cytosine at position 74407, a guanine at position 77398, an adenine at position 93060 and an adenine at position 97627. A threonine at amino acid position 98 in an *APOB* polypeptide was associated with increased risk of osteoarthritis (i.e., an isoleucine to threonine non-synonymous variation).

[0026] Polymorphic variants in and around the *IL1RL2* locus were tested for association with osteoarthritis. These include polymorphic variants at positions in SEQ ID NO: 3 selected from the group consisting of 225, 509, 860, 874, 939, 1483, 1798, 2189, 2215, 2282, 2340, 2963, 3369, 3481, 3564, 3653, 4860, 4941, 4975, 5321, 5346, 5541, 5633, 6007, 6317, 6378, 6382, 6426, 6479, 6641, 6703, 6705, 7963, 8525, 8526, 8598, 8624, 8883, 8980, 13578, 16135, 16141, 16642, 16931, 17004, 17009, 17010, 18713, 18853, 20783, 21335, 22180, 22268, 22285, 25378, 25906, 26015, 26475, 26798, 27042, 27649, 27827, 27873, 28122, 28202, 28232, 28240, 29546, 29748, 30054, 30646, 31149, 36912, 36936, 37184, 39064, 39343, 40868, 40917, 41113, 47343, 47806, 47911, 48009, 48621, 49245, 49247, 49299, 49302, 49514, 49626, 49791, 50010, 50294, 51482, 51556, 51855, 51956, 52155, 52448, 52458, 52511, 52607, 54049, 54224, 54567, 55052, 55857, 55941, 56120, 56349, 56727, 57232, 58806, 61181, 63808, 64526, 64865, 64928, 64966, 65080, 65690, 66228, 66982, 72511, 74170, 74264, 74333, 74502, 74741, 75321, 82558, 85366, 85469, 86485, 87687, 89463, 89660, 95718 and 95821. Polymorphic variants at the following positions in SEQ ID NO: 3 in particular were associated with an increased risk of osteoarthritis: 2215, 3369, 16642, 20783, 52155, 55052, 55941, 74333, 74741, 85366, 85469, 87687, 89660 and 95718, where specific embodiments are directed to position 52155. In particular, the

following polymorphic variants in SEQ ID NO: 3 were associated with risk of osteoarthritis: an adenine at position 2215, a deletion at position 3369, a deletion at position 16642, a cytosine at position 20783, a cytosine at position 52155, a cytosine at position 55052, a cytosine at position 55941, a thymine at position 74333, an adenine at position 74741, a deletion at position 85366, a thymine at position 85469, a thymine at position 87687, an adenine at position 89660 and a cytosine at position 95718.

[0027] Polymorphic variants in and around the *ILIRLI* locus were tested for association with osteoarthritis. These include polymorphic variants at positions in SEQ ID NO: 4 selected from the group consisting of 207, 6019, 6414, 7341, 10984, 12351, 13335, 16584, 16737, 23897, 24057, 25145, 25300, 26262, 26312, 26589, 27302, 27358, 27451, 27552, 30731, 32085, 32139, 33184, 42382, 42569, 44823, 45217, 45548, 45601, 45722, 45967, 47367, 47642, 48126, 49218, 49274, 49433, 49610, 51282, 51466, 53757, 53960, 54031, 54574, 55679, 56100, 56182, 59817, 60533, 60656, 72209, 72778, 74293, 77335, 78029, 78374, 78421, 78434, 79174, 79397, 79562, 79700, 79730, 79904, 79920, 79938, 79972, 80125, 80368, 83484, 85536, 85829, 86425, 88083, 88770, 90622, 90924, 91634, 92029, 95152, 95348, 96145, 96793, 97015, 97064, 97711, 97855 and 98708. Polymorphic variants at the following positions in SEQ ID NO: 4 in particular were associated with an increased risk of osteoarthritis: 6414, 51282, 54574, 78374, 92029 and 96793, where specific embodiments are directed to position 54574. In particular, the following polymorphic variants in SEQ ID NO: 4 were associated with risk of osteoarthritis: an adenine at position 6414, an adenine at position 51282, a cytosine at position 54574, a thymine at position 92029 and an adenine at position 96793.

[0028] Polymorphic variants in and around the *WASPIP* locus were tested for association with osteoarthritis. These include polymorphic variants at positions in SEQ ID NO: 5 selected from the group consisting of 209, 5908, 7460, 7733, 7855, 7904, 8869, 9480, 13820, 15152, 17713, 17804, 18220, 19083, 19123, 19605, 20247, 20592, 21907, 23273, 23299, 23623, 23669, 23844, 24190, 24486, 24896, 25118, 30551, 30844, 30900, 30942, 31699, 32081, 35078, 36196, 36541, 38356, 45578, 49634, 49774, 51119, 51181, 51652, 54467, 55762, 55999, 57865, 66613, 68377, 69754, 72859, 76512, 76717, 77722, 80998, 82033, 89658, 89960, 94155 and 95679. Polymorphic variants at the following positions in SEQ ID NO: 5 in particular were associated with an increased risk of osteoarthritis: 19083, 30900, 38356, 76512 and 94155, where specific embodiments are directed to positions 30900, 76512 and/or 94155. In particular, the following polymorphic variants in SEQ ID NO: 5 were associated with risk of osteoarthritis: a thymine at position 19083, a guanine at position 30900, an adenine at position 38356, an adenine at position 76512 and an adenine at position 94155.

[0029] Polymorphic variants in and around the *ADAMTS2* locus were tested for association with osteoarthritis. These include polymorphic variants at positions in SEQ ID NO: 6 selected from the group consisting of 210, 3608, 3609, 4318, 5593, 5629, 5639, 5640, 8943, 17968, 19887, 21034, 21085, 21596, 23379, 23432, 24007, 26121, 26273, 26755, 27411, 27710, 27842, 28379, 29603, 31232, 31504, 32583, 32794, 32840, 33044, 33150, 33218, 33513, 33959, 34486, 36289, 36570, 38247, 38477, 38518, 38529, 38667, 39781, 39856, 39927, 40506, 41869, 42452, 44788, 46059, 46846, 47712, 48796, 49441, 49602, 49723, 50050, 50171, 50477, 50818, 50833, 50881, 50882, 51386, 51534, 52317, 52368,

52970, 53023, 53356, 53882, 54553, 55475, 55530, 55691, 55848, 55879, 56316, 56911, 57320, 57391, 57437, 57478, 57500, 59111, 59333, 59715, 59804, 59851, 59929, 60052, 60240, 60359, 60381, 60456, 60724, 60875, 60968, 60978, 60998, 61557, 62091, 62645, 62943, 63131, 63145, 63406, 63427, 63554, 63661, 64093, 64153, 64409, 64544, 65257, 65626, 65739, 66392, 66720, 69177, 69336, 69636, 69823, 69928, 70547, 70633, 71805, 72181, 72200, 72474, 72567, 72973, 73468, 73889, 75730, 75970, 76114, 76342, 76449, 76465, 76791, 78042, 80758, 80778, 81356, 81576, 81689, 81759, 81950, 82562, 83591, 83700, 83821, 83842, 83923, 83929, 84021, 84175, 84417, 84747, 85746, 86129, 86335, 87315, 87648, 87764, 87770, 88221, 90474, 91148, 91150, 91160, 91733, 91772, 91785, 93140, 93148, 96080, 96157, 96313, 96759, 97026, 97320, 97732, 98713, 99707, 99959, 100009, 100020, 100065, 100086, 101270, 101276, 101371, 101376, 101439, 101820, 102392, 102602, 102604, 102896, 189104, 189134 and 189205. Polymorphic variants at the following positions in SEQ ID NO: 6 in particular were associated with an increased risk of osteoarthritis: 5640, 33150, 38247, 38529, 46846, 49723, 50050, 63427, 73889, 189104 and rs428901, where specific embodiments are directed to positions 46846, 73889, 189104 and/or rs428901. In particular, the following polymorphic variants in SEQ ID NO: 6 were associated with risk of osteoarthritis: a cytosine at position 5640, a cytosine at position 33150, an adenine at position 38247, a thymine at position 38529, an adenine at position 46846, a cytosine at position 49723, a cytosine at position 50050, a cytosine at position 63427, a guanine at position 73889, a thymine at position 189104, and an adenine at position rs428901.

[0030] Polymorphic variants in and around the *BVES* locus were tested for association with osteoarthritis. These include polymorphic variants at positions in SEQ ID NO: 7 selected from the group consisting of 241, 801, 899, 2091, 2290, 2440, 4959, 7914, 7969, 7972, 10831, 12399, 13841, 14461, 14680, 16808, 18231, 18394, 18505, 18684, 19257, 20263, 20656, 21499, 21563, 21612, 21834, 22406, 22408, 22685, 23303, 23306, 25139, 25211, 25364, 25381, 25414, 25835, 26214, 27224, 27526, 27934, 28550, 29015, 29879, 29979, 30030, 30585, 31753, 31934, 33227, 33228, 35172, 36901, 36921, 36932, 37061, 37570, 38745, 38970, 39725, 40070, 40460, 41470, 41562, 41956, 42047, 42280, 42358, 42629, 43075, 43387, 43393, 43438, 44115, 44537, 45642, 46629, 47496, 47515, 48329, 48862, 48908, 49038, 49080, 50204, 50404, 50426, 50531, 50840, 50964, 50971, 51378, 52610, 53906, 53951, 54111, 54149, 55563, 55999, 58415, 58961, 60447, 61377, 61528, 61606, 62140, 62461, 63826, 64950, 65076, 66121, 66406, 67051, 68860, 69014, 70796, 72325, 73414, 75258, 76347, 76839, 77358, 77822, 77946, 80002, 80024, 80285, 80397, 82075, 82153, 83981, 84184, 85089, 85288, 85330, 85581, 85642, 86433, 86904, 88391, 89042, 90828, 92676, 92881, 94227, 94585, 94616, 94712, 94738, 95253, 95522, 95869 and 97856. Polymorphic variants at the following positions in SEQ ID NO: 7 in particular were associated with an increased risk of osteoarthritis: 25414, 25835, 38970, 41470, 44115, 47496, 49038, 50204, 50840, 50964, 50971, 53906, 54149, 58415, 70796, 72325, 75258, 77822, 80002, 85288, 85581, 86904, 90828, 94616, 94712, 95869 and 97856. In particular, the following polymorphic variants in SEQ ID NO: 7 were associated with risk of osteoarthritis: an adenine at position 25414, a cytosine at position 25835, an adenine at position 38970, an adenine at position 41470, an adenine at position 44115, a guanine at position 47496, a cytosine at position 49038, an adenine at position 50204, a

thymine at position 50840, a cytosine at position 50964, a cytosine at position 50971, an adenine at position 53906, a guanine at position 54149, a guanine at position 58415, a thymine at position 70796, a guanine at position 72325, a cytosine at position 75258, an adenine at position 77822, an adenine at position 80002, an adenine at position 85288, an adenine at position 85581, a guanine at position 86904, a guanine at position 90828, an adenine thymine adenine adenine sequence at position 94616, a cytosine at position 94712, a guanine at position 95869 and a cytosine at position 97856.

[0031] Polymorphic variants in and around the *TM7SF3* locus were tested for association with osteoarthritis. These include polymorphic variants at positions in SEQ ID NO: 8 selected from the group consisting of 230, 231, 5330, 6334, 11372, 11456, 11501, 13393, 16666, 17596, 19710, 19800, 20297, 20967, 32514, 33159, 37600, 41259, 41329, 50060, 53292, 53393, 56417, 56435, 58847, 59595, 59661, 60355, 60407, 62357, 68230, 68516, 69055, 72603, 73928, 85897 and 91554. Polymorphic variants at the following positions in SEQ ID NO: 8 in particular were associated with an increased risk of osteoarthritis: 56435, 59595, 53292, 33159 and 41329, with specific embodiments directed to positions 56435 and/or 59595. In particular, the following polymorphic variants in SEQ ID NO: 8 were associated with risk of osteoarthritis: a thymine thymine repeat at position 56435, a thymine at position 59595, a cytosine at position 53292, a guanine at position 33159 and a thymine at position 41329.

[0032] Polymorphic variants in and around the *LOXLI* locus were tested for association with osteoarthritis. These include polymorphic variants at positions in SEQ ID NO: 10 selected from the group consisting of 213, 249, 1824, 2057, 2306, 2869, 3976, 4288, 4290, 4434, 5298, 5467, 8486, 8487, 8831, 9036, 9058, 9131, 9732, 9862, 10191, 10270, 16167, 17620, 17751, 17764, 17787, 19401, 21021, 21902, 22173, 22416, 22653, 24945, 25011, 28563, 48574, 48710, 48880, 50194, 56343, 56455, 56729, 56759, 56895, 57036, 57702, 62515, 62629, 63501, 63547, 64876, 65073, 67149, 67549, 71660, 71906 and 71911. A polymorphic variant at position 65073 in SEQ ID NO: 10, often a guanine, in particular was associated with an increased risk of osteoarthritis.

[0033] Polymorphic variants in and around the *CASPR4* locus were tested for association with osteoarthritis. These include polymorphic variants at positions in SEQ ID NO: 11 selected from the group consisting of 205, 866, 4212, 5934, 11486, 16969, 22509, 22796, 28097, 28626, 28853, 28873, 30155, 30827, 31956, 32404, 32944, 35205, 35227, 35781, 41052, 45051, 46039, 47276, 47678, 47716, 51014, 54408, 54596, 56853, 61851, 62016, 62461, 68257, 69793, 73976, 73999, 74053, 75315, 75729, 76466, 77216, 77217, 79239, 80825, 81060, 81097, 81426, 84787, 84896, 85165, 86502, 86753, 86941, 88787 and 95598. Polymorphic variants at the following positions in SEQ ID NO: 11 in particular were associated with an increased risk of osteoarthritis: 47716 and 69793. In particular, the following polymorphic variants in SEQ ID NO: 11 were associated with risk of osteoarthritis: an adenine at position 47716 and a thymine at position 69793.

[0034] Polymorphic variants in and around the *APOL3* locus were tested for association with osteoarthritis. These include polymorphic variants at positions in SEQ ID NO: 13 selected from the group consisting of 201, 425, 1095, 2201, 7879, 8395, 8461, 9503, 10304, 10695, 16300, 16444, 17591, 17988, 19116, 19358, 20300, 20669, 20891, 21451, 21978, 22785, 24248, 24770, 24844, 25066, 25096,

25309, 25344, 25529, 25537, 25554, 27963, 28134, 28356, 29648, 29986, 30217, 30267, 30315, 30585, 30724, 30897, 30931, 31080, 31246, 31373, 31463, 31467, 32188, 32288, 32520, 32594, 32657, 32677, 32764, 32784, 32830, 32872, 33121, 33348, 33952, 34184, 34361, 35026, 35192, 35600, 36033, 36289, 38869, 39629, 40530, 41621, 42379, 42802, 42865, 43644, 45051, 45828, 45829, 46257, 47286, 47427, 47963, 48013, 48229, 48282, 48376, 48404, 49900, 52699, 52897, 53414, 53487, 54112, 55492, 59766, 60307, 60701, 60952, 61401, 62379, 62870, 62879, 63499, 64284, 64408, 64760, 65230, 66127, 6634, 66686, 66694, 67113, 67257, 67403, 67609, 68418, 68610, 69629, 70024, 70848, 71428, 71553, 71633, 71768, 71769, 73039, 73325, 73412, 73547, 73769, 73806, 74467, 74472, 74473, 74482, 74494, 74592, 74670, 74672, 74714, 74723, 74749, 74861, 74892, 74893, 75176, 75705, 75989, 76027, 77949, 77974, 78167, 78310, 78415, 78575, 78590, 78709, 78875, 79864, 81316, 81320, 81409, 81737, 81843, 82102, 82833, 83461, 83624, 83660, 83701, 83708, 83782, 85707, 85717, 86486, 86833, 87115, 87234, 87479, 87561, 87604, 87674, 87958, 87992, 88019, 88074, 88079, 88115, 88118, 88120, 88135, 88142, 88143, 88149, 88340, 88344, 88512, 88521, 88650, 88827, 89230, 89236, 90754, 90984, 91110, 92026, 92954, 93375, 93794, 94937, 95068, 96188, 97092 and 98812. Polymorphic variants at the following positions in SEQ ID NO: 13 in particular were associated with an increased risk of osteoarthritis: 20300, 46257, 87958, 89236, 30267, 32657, 36289, 38869, 45051, 54112, 60307, 63499, 20891, 52699, 71768, with specific embodiments directed to position 46257. In particular, the following polymorphic variants in SEQ ID NO: 13 were associated with risk of osteoarthritis: an adenine at position 20300, a thymine at position 46257, an adenine at position 89236, a guanine at position 30267, an adenine at position 32657, a cytosine at position 36289, a guanine at position 38869, a thymine at position 45051, a guanine at position 54112, an adenine at position 60307, a thymine at position 63499, a guanine at position 20891, a guanine at position 52699, and a cytosine at position 71768.

[0035] Based in part upon analyses summarized in Figures 1A-1J, regions with significant association have been identified in regions associated with osteoarthritis. Any polymorphic variants associated with osteoarthritis in a region of significant association can be utilized for embodiments described herein. For example, polymorphic variants in a region spanning positions 21233000 to 21243000 (approximately 10,000 nucleotides in length) in a *APOB* locus, a region spanning chromosome positions 102456500 to 102471500 (approximately 15,000 nucleotides in length) in a *ILIRL2* locus, a region spanning chromosome positions 102570000 to 102583000 (approximately 13,000 nucleotides in length) in a *ILIRL1* locus, a region spanning chromosome positions 175647734 to 175655734 (approximately 8,000 nucleotides in length) in a *WASPIP* locus, a region spanning chromosome positions 178746000 to 178751000 (approximately 5,000 nucleotides in length) in a *ADAMTS2* locus, a region spanning chromosome positions 105595000 to 105615000 (approximately 20,000 nucleotides in length) in a *BVES* locus, in a region approximately 14,000 nucleotides in length spanning chromosome positions 27052000 to 27066000 in a *TM7SF3* locus, a region spanning chromosome positions 71957600 to 71962600 (approximately 5,000 nucleotides in length) in a *LOXLI* locus, a region spanning chromosome positions 76221000 to 76226000 (approximately 5,000 nucleotides in length) in a *CASPR4* locus, and a region approximately 5000 nucleotides in length and

spanning chromosome positions 3 4828750 and 34833750 in an *APOL3* locus, have significant association (chromosome positions are within NCBI's Genome build 34).

Additional Polymorphic Variants Associated with Osteoarthritis

[0036] Also provided is a method for identifying polymorphic variants proximal to an incident, founder polymorphic variant associated with osteoarthritis. Thus, featured herein are methods for identifying a polymorphic variation associated with osteoarthritis that is proximal to an incident polymorphic variation associated with osteoarthritis, which comprises identifying a polymorphic variant proximal to the incident polymorphic variant associated with osteoarthritis, where the incident polymorphic variant is in a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXLI*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B. The nucleotide sequence often comprises a polynucleotide sequence selected from the group consisting of (a) a polynucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; (b) a polynucleotide sequence that encodes a polypeptide having an amino acid sequence encoded by a polynucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; and (c) a polynucleotide sequence that encodes a polypeptide having an amino acid sequence that is 90% or more identical to an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B or a polynucleotide sequence 90% or more identical to the polynucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B. The presence or absence of an association of the proximal polymorphic variant with osteoarthritis then is determined using a known association method, such as a method described in the Examples hereafter. In an embodiment, the incident polymorphic variant is a polymorphic variant associated with osteoarthritis described herein. In another embodiment, the proximal polymorphic variant identified sometimes is a publicly disclosed polymorphic variant, which for example, sometimes is published in a publicly available database. In other embodiments, the polymorphic variant identified is not publicly disclosed and is discovered using a known method, including, but not limited to, sequencing a region surrounding the incident polymorphic variant in a group of nucleic samples. Thus, multiple polymorphic variants proximal to an incident polymorphic variant are associated with osteoarthritis using this method.

[0037] The proximal polymorphic variant often is identified in a region surrounding the incident polymorphic variant. In certain embodiments, this surrounding region is about 50 kb flanking the first polymorphic variant (*e.g.* about 50 kb 5' of the first polymorphic variant and about 50 kb 3' of the first polymorphic variant), and the region sometimes is composed of shorter flanking sequences, such as flanking sequences of about 40 kb, about 30 kb, about 25 kb, about 20 kb, about 15 kb, about 10 kb, about 7 kb, about 5 kb, or about 2 kb 5' and 3' of the incident polymorphic variant. In other embodiments, the region is composed of longer flanking sequences, such as flanking sequences of about 55 kb, about 60 kb, about 65 kb, about 70 kb, about 75 kb, about 80 kb, about 85 kb, about 90 kb, about 95 kb, or about 100 kb 5' and 3' of the incident polymorphic variant.

[0038] In certain embodiments, polymorphic variants associated with osteoarthritis are identified iteratively. For example, a first proximal polymorphic variant is associated with osteoarthritis using the methods described above and then another polymorphic variant proximal to the first proximal polymorphic variant is identified (*e.g.*, publicly disclosed or discovered) and the presence or absence of an association of one or more other polymorphic variants proximal to the first proximal polymorphic variant with osteoarthritis is determined.

[0039] The methods described herein are useful for identifying or discovering additional polymorphic variants that may be used to further characterize a gene, region or loci associated with a condition, a disease (*e.g.*, osteoarthritis), or a disorder. For example, allelotyping or genotyping data from the additional polymorphic variants may be used to identify a functional mutation or a region of linkage disequilibrium. In certain embodiments, polymorphic variants identified or discovered within a region comprising the first polymorphic variant associated with osteoarthritis are genotyped using the genetic methods and sample selection techniques described herein, and it can be determined whether those polymorphic variants are in linkage disequilibrium with the first polymorphic variant. The size of the region in linkage disequilibrium with the first polymorphic variant also can be assessed using these genotyping methods. Thus, provided herein are methods for determining whether a polymorphic variant is in linkage disequilibrium with a first polymorphic variant associated with osteoarthritis, and such information can be used in prognosis/diagnosis methods described herein.

Isolated Nucleic Acids

[0040] Featured herein are isolated *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXLI*, *CASPR4* or *APOL3* nucleic acid variants depicted in SEQ ID NO: 1-13, SEQ ID NO: 14-36 or referenced in Table B, and substantially identical nucleic acids thereof. A nucleic acid variant may be represented on one or both strands in a double-stranded nucleic acid or on one chromosomal complement (heterozygous) or both chromosomal complements (homozygous).

[0041] *ADAMTS2* exists in two forms, a "long" form comprising a molecule approximately 130 kDa in length (*e.g.*, SEQ ID NO: 21 for cDNA sequence and SEQ ID NO: 44 for amino acid sequence), and a "short" form comprising a molecule approximately 70 kDa in length (*e.g.*, SEQ ID NO: 22 for cDNA sequence and SEQ ID NO: 45 for amino acid sequence). Provided herein are polynucleotide sequences encoding both the short and long forms of *ADAMTS2*.

[0042] As used herein, the term "nucleic acid" includes DNA molecules (*e.g.*, a complementary DNA (cDNA) and genomic DNA (gDNA)) and RNA molecules (*e.g.*, mRNA, rRNA, siRNA and tRNA) and analogs of DNA or RNA, for example, by use of nucleotide analogs. The nucleic acid molecule can be single-stranded and it is often double-stranded. The term "isolated or purified nucleic acid" refers to nucleic acids that are separated from other nucleic acids present in the natural source of the nucleic acid. For example, with regard to genomic DNA, the term "isolated" includes nucleic acids which are separated from the chromosome with which the genomic DNA is naturally associated. An "isolated" nucleic acid is often free of sequences which naturally flank the nucleic acid (*i.e.*, sequences

located at the 5' and/or 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of 5' and/or 3' nucleotide sequences which flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. As used herein, the term "gene" refers to a nucleotide sequence that encodes a polypeptide.

[0043] Also included herein are nucleic acid fragments. These fragments often have a nucleotide sequence identical to a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B, a nucleotide sequence substantially identical to a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B, or a nucleotide sequence that is complementary to the foregoing. The nucleic acid fragment may be identical, substantially identical or homologous to a nucleotide sequence in an exon or an intron in a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B, and may encode a domain or part of a domain of a polypeptide. Sometimes, the fragment will comprises one or more of the polymorphic variations described herein as being associated with osteoarthritis. The nucleic acid fragment is often 50, 100, or 200 or fewer base pairs in length, and is sometimes about 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 2000, 3000, 4000, 5000, 10000, 15000, or 20000 base pairs in length. A nucleic acid fragment that is complementary to a nucleotide sequence identical or substantially identical to a nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B and hybridizes to such a nucleotide sequence under stringent conditions is often referred to as a "probe." Nucleic acid fragments often include one or more polymorphic sites, or sometimes have an end that is adjacent to a polymorphic site as described hereafter.

[0044] An example of a nucleic acid fragment is an oligonucleotide. As used herein, the term "oligonucleotide" refers to a nucleic acid comprising about 8 to about 50 covalently linked nucleotides, often comprising from about 8 to about 35 nucleotides, and more often from about 10 to about 25 nucleotides. The backbone and nucleotides within an oligonucleotide may be the same as those of naturally occurring nucleic acids, or analogs or derivatives of naturally occurring nucleic acids, provided that oligonucleotides having such analogs or derivatives retain the ability to hybridize specifically to a nucleic acid comprising a targeted polymorphism. Oligonucleotides described herein may be used as hybridization probes or as components of prognostic or diagnostic assays, for example, as described herein.

[0045] Oligonucleotides are typically synthesized using standard methods and equipment, such as the ABI™3900 High Throughput DNA Synthesizer and the EXPEDITE™ 8909 Nucleic Acid Synthesizer, both of which are available from Applied Biosystems (Foster City, CA). Analogs and derivatives are exemplified in U.S. Pat. Nos. 4,469,863; 5,536,821; 5,541,306; 5,637,683; 5,637,684; 5,700,922; 5,717,083; 5,719,262; 5,739,308; 5,773,601; 5,886,165; 5,929,226; 5,977,296; 6,140,482; WO 00/56746; WO 01/14398, and related publications. Methods for synthesizing oligonucleotides

comprising such analogs or derivatives are disclosed, for example, in the patent publications cited above and in U.S. Pat. Nos. 5,614,622; 5,739,314; 5,955,599; 5,962,674; 6,117,992; in WO 00/75372; and in related publications.

[0046] Oligonucleotides may also be linked to a second moiety. The second moiety may be an additional nucleotide sequence such as a tail sequence (*e.g.*, a polyadenosine tail), an adapter sequence (*e.g.*, phage M13 universal tail sequence), and others. Alternatively, the second moiety may be a non-nucleotide moiety such as a moiety which facilitates linkage to a solid support or a label to facilitate detection of the oligonucleotide. Such labels include, without limitation, a radioactive label, a fluorescent label, a chemiluminescent label, a paramagnetic label, and the like. The second moiety may be attached to any position of the oligonucleotide, provided the oligonucleotide can hybridize to the nucleic acid comprising the polymorphism.

Uses for Nucleic Acid Sequence

[0047] Nucleic acid coding sequences may be used for diagnostic purposes for detection and control of polypeptide expression. Also, included herein are oligonucleotide sequences such as antisense RNA, small-interfering RNA (siRNA) and DNA molecules and ribozymes that function to inhibit translation of a polypeptide. Antisense techniques and RNA interference techniques are known in the art and are described herein.

[0048] Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. The mechanism of ribozyme action involves sequence specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, hammerhead motif ribozyme molecules may be engineered that specifically and efficiently catalyze endonucleolytic cleavage of RNA sequences corresponding to or complementary to *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPI*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequences or other nucleotide sequences referenced in Table B. Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites which include the following sequences, GUA, GUU and GUC. Once identified, short RNA sequences of between fifteen (15) and twenty (20) ribonucleotides corresponding to the region of the target gene containing the cleavage site may be evaluated for predicted structural features such as secondary structure that may render the oligonucleotide sequence unsuitable. The suitability of candidate targets may also be evaluated by testing their accessibility to hybridization with complementary oligonucleotides, using ribonuclease protection assays.

[0049] Antisense RNA and DNA molecules, siRNA and ribozymes may be prepared by any method known in the art for the synthesis of RNA molecules. These include techniques for chemically synthesizing oligodeoxyribonucleotides well known in the art such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense RNA molecule. Such DNA sequences may be incorporated into a wide variety of vectors which incorporate suitable RNA polymerase promoters such

as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into cell lines.

[0050] DNA encoding a polypeptide also may have a number of uses for the diagnosis of diseases, including osteoarthritis, resulting from aberrant expression of a target gene described herein. For example, the nucleic acid sequence may be used in hybridization as says of biopsies or autopsies to diagnose abnormalities of expression or function (*e.g.*, Southern or Northern blot analysis, *in situ* hybridization assays).

[0051] In addition, the expression of a polypeptide during embryonic development may also be determined using nucleic acid encoding the polypeptide. As addressed, *infra*, production of functionally impaired polypeptide is the cause of various disease states, such as osteoarthritis. *In situ* hybridizations using polypeptide as a probe may be employed to predict problems related to osteoarthritis. Further, as indicated, *infra*, administration of human active polypeptide, recombinantly produced as described herein, may be used to treat disease states related to functionally impaired polypeptide. Alternatively, gene therapy approaches may be employed to remedy deficiencies of functional polypeptide or to replace or compete with dysfunctional polypeptide.

Expression Vectors, Host Cells, and Genetically Engineered Cells

[0052] Provided herein are nucleic acid vectors, often expression vectors, which contain a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B, or a substantially identical sequence thereof. As used herein, the term “vector” refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked and can include a plasmid, cosmid, or viral vector. The vector can be capable of autonomous replication or it can integrate into a host DNA. Viral vectors may include replication defective retroviruses, adenoviruses and adeno-associated viruses for example.

[0053] A vector can include a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B in a form suitable for expression of an encoded target polypeptide or target nucleic acid in a host cell. A “target polypeptide” is a polypeptide encoded by a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B, or a substantially identical nucleotide sequence thereof. The recombinant expression vector typically includes one or more regulatory sequences operatively linked to the nucleic acid sequence to be expressed. The term “regulatory sequence” includes promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence, as well as tissue-specific regulatory and/or inducible sequences. The design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of polypeptide desired, and the

like. Expression vectors can be introduced into host cells to produce target polypeptides, including fusion polypeptides.

[0054] Recombinant expression vectors can be designed for expression of target polypeptides in prokaryotic or eukaryotic cells. For example, target polypeptides can be expressed in *E. coli*, insect cells (e.g., using baculovirus expression vectors), yeast cells, or mammalian cells. Suitable host cells are discussed further in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

[0055] Expression of polypeptides in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion polypeptides. Fusion vectors add a number of amino acids to a polypeptide encoded therein, usually to the amino terminus of the recombinant polypeptide. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant polypeptide; 2) to increase the solubility of the recombinant polypeptide; and 3) to aid in the purification of the recombinant polypeptide by acting as a ligand in affinity purification. Often, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant polypeptide to enable separation of the recombinant polypeptide from the fusion moiety subsequent to purification of the fusion polypeptide. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith & Johnson, *Gene* 67: 31-40 (1988)), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding polypeptide, or polypeptide A, respectively, to the target recombinant polypeptide.

[0056] Purified fusion polypeptides can be used in screening assays and to generate antibodies specific for target polypeptides. In a therapeutic embodiment, fusion polypeptide expressed in a retroviral expression vector is used to infect bone marrow cells that are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time has passed (e.g., six (6) weeks).

[0057] Expressing the polypeptide in host bacteria with an impaired capacity to proteolytically cleave the recombinant polypeptide is often used to maximize recombinant polypeptide expression (Gottesman, S., *Gene Expression Technology: Methods in Enzymology, Academic Press, San Diego, California* 185: 119-128 (1990)). Another strategy is to alter the nucleotide sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, *Nucleic Acids Res.* 20: 2111-2118 (1992)). Such alteration of nucleotide sequences can be carried out by standard DNA synthesis techniques.

[0058] When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. Recombinant mammalian expression vectors are

often capable of directing expression of the nucleic acid in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Non-limiting examples of suitable tissue-specific promoters include an albumin promoter (liver-specific; Pinkert *et al.*, *Genes Dev.* 1: 268-277 (1987)), lymphoid-specific promoters (Calame & Eaton, *Adv. Immunol.* 43: 235-275 (1988)), promoters of T cell receptors (Winoto & Baltimore, *EMBO J.* 8: 729-733 (1989)) promoters of immunoglobulins (Banerji *et al.*, *Cell* 33: 729-740 (1983); Queen & Baltimore, *Cell* 33: 741-748 (1983)), neuron-specific promoters (e.g., the neurofilament promoter; Byrne & Ruddle, *Proc. Natl. Acad. Sci. USA* 86: 5473-5477 (1989)), pancreas-specific promoters (Edlund *et al.*, *Science* 230: 912-916 (1985)), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are sometimes utilized, for example, the murine hox promoters (Kessel & Gruss, *Science* 249: 374-379 (1990)) and the α -fetoprotein promoter (Campes & Tilghman, *Genes Dev.* 3: 537-546 (1989)).

[0059] A *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleic acid referenced in Table B also may be cloned into an expression vector in an antisense orientation. Regulatory sequences (e.g., viral promoters and/or enhancers) operatively linked to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleic acid referenced in Table B cloned in the antisense orientation can be chosen for directing constitutive, tissue specific or cell type specific expression of antisense RNA in a variety of cell types. Antisense expression vectors can be in the form of a recombinant plasmid, phagemid or attenuated virus. For a discussion of the regulation of gene expression using antisense genes see, e.g., Weintraub *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) (1986).

[0060] Also provided herein are host cells that include a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B within a recombinant expression vector or a fragment of such a nucleotide sequence which facilitate homologous recombination into a specific site of the host cell genome. The terms "host cell" and "recombinant host cell" are used interchangeably herein. Such terms refer not only to the particular subject cell but rather also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein. A host cell can be any prokaryotic or eukaryotic cell. For example, a target polypeptide can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

[0061] Vectors can be introduced into host cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (e.g., DNA) into a host cell,

including calcium phosphate or calcium chloride co-precipitation, transduction/infection, DEAE-dextran-mediated transfection, lipofection, or electroporation.

[0062] A host cell provided herein can be used to produce (*i.e.*, express) a target polypeptide or a substantially identical polypeptide thereof. Accordingly, further provided are methods for producing a target polypeptide using host cells described herein. In one embodiment, the method includes culturing host cells into which a recombinant expression vector encoding a target polypeptide has been introduced in a suitable medium such that a target polypeptide is produced. In another embodiment, the method further includes isolating a target polypeptide from the medium or the host cell.

[0063] Also provided are cells or purified preparations of cells which include a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* transgene, or other transgene in Table B, or which otherwise misexpress target polypeptide. Cell preparations can consist of human or non-human cells, *e.g.*, rodent cells, *e.g.*, mouse or rat cells, rabbit cells, or pig cells. In preferred embodiments, the cell or cells include a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* transgene or other transgene referenced in Table B (*e.g.*, a heterologous form of a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* gene or other gene referenced in Table B, such as a human gene expressed in non-human cells). The transgene can be misexpressed, *e.g.*, overexpressed or underexpressed. In other preferred embodiments, the cell or cells include a gene which misexpresses an endogenous target polypeptide (*e.g.*, expression of a gene is disrupted, also known as a knockout). Such cells can serve as a model for studying disorders which are related to mutated or mis-expressed alleles or for use in drug screening. Also provided are human cells (*e.g.*, a hematopoietic stem cells) transfected with a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleic acid referenced in Table B.

[0064] Also provided are cells or a purified preparation thereof (*e.g.*, human cells) in which an endogenous *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleic acid referenced in Table B is under the control of a regulatory sequence that does not normally control the expression of the endogenous gene. The expression characteristics of an endogenous gene within a cell (*e.g.*, a cell line or microorganism) can be modified by inserting a heterologous DNA regulatory element into the genome of the cell such that the inserted regulatory element is operably linked to the corresponding endogenous gene. For example, an endogenous corresponding gene (*e.g.*, a gene which is "transcriptionally silent," not normally expressed, or expressed only at very low levels) may be activated by inserting a regulatory element which is capable of promoting the expression of a normally expressed gene product in that cell. Techniques such as targeted homologous recombinations, can be used to insert the heterologous DNA as described in, *e.g.*, Chappel, US 5,272,071; WO 91/06667, published on May 16, 1991.

Transgenic Animals

[0065] Non-human transgenic animals that express a heterologous target polypeptide (*e.g.*, expressed from a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleic acid referenced in Table B, or substantially identical sequence thereof) can be generated. Such animals are useful for studying the function and/or activity of a target polypeptide and for identifying and/or evaluating modulators of the activity of *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acids, other nucleic acids referenced in Table B, and encoded polypeptides. As used herein, a “transgenic animal” is a non-human animal such as a mammal (*e.g.*, a non-human primate such as chimpanzee, baboon, or macaque; an ungulate such as an equine, bovine, or caprine; or a rodent such as a rat, a mouse, or an Israeli sand rat), a bird (*e.g.*, a chicken or a turkey), an amphibian (*e.g.*, a frog, salamander, or newt), or an insect (*e.g.*, *Drosophila melanogaster*), in which one or more of the cells of the animal includes a transgene. A transgene is exogenous DNA or a rearrangement (*e.g.*, a deletion of endogenous chromosomal DNA) that is often integrated into or occurs in the genome of cells in a transgenic animal. A transgene can direct expression of an encoded gene product in one or more cell types or tissues of the transgenic animal, and other transgenes can reduce expression (*e.g.*, a knockout). Thus, a transgenic animal can be one in which an endogenous nucleic acid homologous to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleic acid referenced in Table B has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal (*e.g.*, an embryonic cell of the animal) prior to development of the animal.

[0066] Intronic sequences and polyadenylation signals can also be included in the transgene to increase expression efficiency of the transgene. One or more tissue-specific regulatory sequences can be operably linked to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B to direct expression of an encoded polypeptide to particular cells. A transgenic founder animal can be identified based upon the presence of a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B in its genome and/or expression of encoded mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B can further be bred to other transgenic animals carrying other transgenes.

[0067] Target polypeptides can be expressed in transgenic animals or plants by introducing, for example, a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleic acid referenced in Table B into the genome of an animal that encodes the target polypeptide. In preferred embodiments the nucleic acid is placed under the control of

a tissue specific promoter, *e.g.*, a milk or egg specific promoter, and recovered from the milk or eggs produced by the animal. Also included is a population of cells from a transgenic animal.

Target Polypeptides

[0068] Also featured herein are isolated target polypeptides, which are encoded by a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or a nucleotide sequence referenced in Table B (*e.g.*, SEQ ID NO: 14-36 or a sequence referenced in Table B), or a substantially identical nucleotide sequence thereof. Examples of *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* polypeptides are set forth in SEQ ID NO: 37-55. The term “polypeptide” as used herein includes proteins and peptides. An “isolated” or “purified” polypeptide or protein is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. In one embodiment, the language “substantially free” means preparation of a target polypeptide having less than about 30%, 20%, 10% and more preferably 5% (by dry weight), of non-target polypeptide (also referred to herein as a “contaminating protein”), or of chemical precursors or non-target chemicals. When the target polypeptide or a biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, specifically, where culture medium represents less than about 20%, sometimes less than about 10%, and often less than about 5% of the volume of the polypeptide preparation. Isolated or purified target polypeptide preparations are sometimes 0.01 milligrams or more or 0.1 milligrams or more, and often 1.0 milligrams or more and 10 milligrams or more in dry weight. In certain embodiments, the *APOL3* polypeptide or polypeptide fragment has *APOL3* biological activity, for example, apolipoprotein activity.

[0069] Further included herein are target polypeptide fragments. The polypeptide fragment may be a domain or part of a domain of a target polypeptide. The polypeptide fragment may have increased, decreased or unexpected biological activity. The polypeptide fragment is often 50 or fewer, 100 or fewer, or 200 or fewer amino acids in length, and is sometimes 300, 400, 500, 600, 700, or 900 or fewer amino acids in length. In certain embodiments, the polypeptide fragment sometimes is amino acids 90-396 of SEQ ID NO: 53; amino acids 19-325 of SEQ ID NO: 54; or amino acids 1-196 of SEQ ID NO: 55. Shown in Table A below are examples of polypeptide fragments, where approximate amino acid positions are shown in parenthesis (*e.g.*, a Pellino domain starts at about amino acid 3 and ends at about amino acid 412). Amino acid sequences can be accessed using information in Table B and in SEQ ID NO: 37-55.

TABLE A

RS_ID	Locus	SEQ ID NO.	Signal Peptide	Domain (amino acid ranges)
910223	<i>PADI2</i>	37	none	
1367117	<i>APOB</i>	38	1-27	Apolipoprotein B48 mature peptide (1-2151) Lipoprotein amino terminal region (46-597)

RS_ID	Locus	SEQ ID NO.	Signal Peptide	Domain (amino acid ranges)
				ATPase involved in DNA repair (2077-2583)
1024791	<i>IL1RL2</i>	39	1-19	Immunoglobulin C-2 Type (36-100; 137-197) TIR Domain (385-535) Neural cell adhesion molecule L1 (<53->295) Transmembrane Domain (336-358)
1465621	<i>WASPIP</i>	43	none	WASP-interacting protein VRP1/WIP (14->63)
1018810	<i>BVES</i>	46	none	Popeye protein conserved region (123-266)
242392	<i>PELI2</i>	48	none	Pellino (3-412)
8818	<i>LOXL1</i>	49	none	Lysyl oxidase (370-574)
1395486	<i>CASPR4</i>	50	none	Neurexin IV domain (3-1308) F5/8 type C domain (57-177) Laminin G domains (374-524; 475->750; 797-941; 1037-1176)
		51	none	Neurexin IV domain (1->721) F5/8 type C domain (29-149) Laminin G domains (169-314; 346-496; 579->662)
512294	<i>GPR50</i>	52	none	7 transmembrane receptor (rhodopsin family) (45..294) Microtubule-associated protein dynactin DCTN1/Glued (462..>587) Syndecan domain (485..>595)

[0070] Interleukin 1 receptor-like 1 isoform 1 (SEQ ID NO: 40) is a member of the interleukin 1 receptor family with no known ligand (orphan receptor). *IL1RL1* exists in soluble (SEQ ID NO: 41-42) and transmembrane forms, suggesting that it may have ligand or ligand scavenging activity. In an embodiment, *IL1RL1* protein agents may be administered to treat or prevent the occurrence of OA. *IL1RL1* protein agents include *IL1RL1* polypeptides or fragments thereof that have *IL1RL1* ligand activity (e.g., recombinant polypeptides of SEQ ID NO: 41-42). In a related embodiment, *IL1RL1* protein agents include *IL1RL1* polypeptides or fragments thereof that have *IL1RL1* ligand scavenging activity (e.g., recombinant polypeptide of SEQ ID NO: 40). Isolated *IL1RL1* polypeptides featured herein include the full-length polypeptide, the mature polypeptide (i.e., the polypeptide without the signal sequence MGFWILAILTILMYSTAA) or a polypeptide fragment containing a domain or part of a *IL1RL1* domain. The polypeptide fragment may have increased, decreased or unexpected biological activity.

[0071] In another embodiment, provided herein are *ADAMTS2* polypeptides having an *ADAMTS2* activity (e.g., a zinc binding activity, a metalloprotease activity, a procollagen II processing or synthesis activity, or a collagen II synthesis activity in vitro or in vivo). In certain embodiments, the polypeptides are *ADAMTS2* proteins including at least one propeptide domain, at least one metalloproteinase domain, at least one disintegrin-like domain, at least one, two, three, and often four thrombospondin domains, and sometimes having a *ADAMTS2* activity, e.g., a *ADAMTS2* activity as described herein. *ADAMTS2*

polypeptides and fragments thereof often have biological activity, such as excising the N-propeptide of type II procollagens. Methods for monitoring and quantifying this biological activity are known (e.g., Colige et al., J. Biol. Chem. 270: 16724-16730 (1995)).

[0072] Human *ADAMTS2* protein (SEQ ID NO: 44-45) includes a signal sequence of about 29 amino acids (from amino acid 1 to about amino acid 29 of SEQ ID NO: 44-45). The *ADAMTS2* protein without the signal sequence can be approximately 1182 amino acid residues in length (from about amino acid 30 to amino acid 1211 of SEQ ID NO: 44) or approximately 485 amino acid residues in length (from about amino acid 30 to amino acid 514 of SEQ ID NO: 45). Human *ADAMTS2* protein includes a “pro” region homologous to the reprotolysin family propeptide, which is typically post-translationally cleaved upon conversion of the inactive (or pro-domain containing) protein to the catalytically active metalloprotease. The prodomain region of human *ADAMTS2* protein corresponds to about amino acids 30 to 251, 30 to 252, 30 to 253, 30 to 254, 30 to 255, 30 to 256, 30 to 257, 30 to 258 or 30 to 259 of SEQ ID NO: 44-45, where it is understood that the active form of *ADAMTS2* does not contain the propeptide domain.

[0073] Upon cleavage, catalytically active mature protein can be approximately 960, 959, 958, 957, 956, 955, 954, 953 or 952 amino acids in length (from about amino acid 252, 253, 254, 255, 256, 257, 258, 259 or 260 to amino acid 1211 of SEQ ID NO: 44) or approximately 261, 260, 259, 258, 257, 256, 255, 254 or 253 amino acid residues in length (from about amino acid 252, 253, 254, 255, 256, 257, 258, 259 or 260 to amino acid 514 of SEQ ID NO: 45).

[0074] Human *ADAMTS2* contains the following regions or other structural features: a signal sequence at about amino acids 1-29 of SEQ ID NO: 44-45; a reprotolysin family propeptide domain located at about amino acid residues 30 to 251, 30 to 252, 30 to 253, 30 to 254, 30 to 255, 30 to 256, 30 to 257, 30 to 258 or 30 to 259 of SEQ ID NO: 44-45; a zinc-metalloprotease catalytic domain at about amino acids 251 to 479, 252 to 479, 253 to 479, 254 to 479, 255 to 479, 256 to 479, 257 to 479, 258 to 479 or 259 to 479 of SEQ ID NO: 44-45; a disintegrin domain at about amino acids 480 to 560 of SEQ ID NO: 44; a cysteine-rich domain at about amino acids 618 to 722 of SEQ ID NO: 44; four thrombospondin motifs-2 motifs at about amino acids 561 to 616, 854 to 912, 914 to 971, and 975 to 1029 of SEQ ID NO: 44; and eight N-glycosylation sites located at about amino acids 112, 251, 949, 993, 1031, 1098, 1145, and 1150 of SEQ ID NO: 44.

[0075] In other embodiments, provided are methods of increasing the synthesis of procollagen II comprising providing or administering to individuals in need of increasing levels of type II collagen the pharmaceutical or physiologically acceptable composition comprising active human *ADAMTS2* protein or fragment thereof, where *ADAMTS2* polypeptide fragments having activity are selected from amino acids 252-1211, 253-1211, 254-1211, 255-1211, 256-1211, 257-1211, 258-1211, 259-1211 or 260-1211 of SEQ ID NO: 4, where it is understood that the active form of *ADAMTS2* does not contain the propeptide domain.

[0076] Substantially identical target polypeptides may depart from the amino acid sequences of target polypeptides in different manners. For example, conservative amino acid modifications may be

introduced at one or more positions in the amino acid sequences of target polypeptides. A “conservative amino acid substitution” is one in which the amino acid is replaced by another amino acid having a similar structure and/or chemical function. Families of amino acid residues having similar structures and functions are well known. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Also, essential and non-essential amino acids may be replaced. A “non-essential” amino acid is one that can be altered without abolishing or substantially altering the biological function of a target polypeptide, whereas altering an “essential” amino acid abolishes or substantially alters the biological function of a target polypeptide. Amino acids that are conserved among target polypeptides are typically essential amino acids. In certain embodiments, the polypeptide includes one or more non-synonymous polymorphic variants associated with osteoarthritis, as described above (*e.g.*, a threonine encoded by rs1367117 in an *APOB* polypeptide).

[0077] Also, target polypeptides may exist as chimeric or fusion polypeptides. As used herein, a target “chimeric polypeptide” or target “fusion polypeptide” includes a target polypeptide linked to a non-target polypeptide. A “non-target polypeptide” refers to a polypeptide having an amino acid sequence corresponding to a polypeptide which is not substantially identical to the target polypeptide, which includes, for example, a polypeptide that is different from the target polypeptide and derived from the same or a different organism. The target polypeptide in the fusion polypeptide can correspond to an entire or nearly entire target polypeptide or a fragment thereof. The non-target polypeptide can be fused to the N-terminus or C-terminus of the target polypeptide.

[0078] Fusion polypeptides can include a moiety having high affinity for a ligand. For example, the fusion polypeptide can be a GST-target fusion polypeptide in which the target sequences are fused to the C-terminus of the GST sequences, or a polyhistidine-target fusion polypeptide in which the target polypeptide is fused at the N- or C-terminus to a string of histidine residues. Such fusion polypeptides can facilitate purification of recombinant target polypeptide. Expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide), and a nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B, or a substantially identical nucleotide sequence thereof, can be cloned into an expression vector such that the fusion moiety is linked in-frame to the target polypeptide. Further, the fusion polypeptide can be a target polypeptide containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression, secretion, cellular internalization, and cellular localization of a target polypeptide can be increased through use of a heterologous signal sequence. Fusion polypeptides can also include all or a part of a serum polypeptide (*e.g.*, an IgG constant region or human serum albumin).

[0079] Target polypeptides can be incorporated into pharmaceutical compositions and administered to a subject *in vivo*. Administration of these target polypeptides can be used to affect the

bioavailability of a substrate of the target polypeptide and may effectively increase target polypeptide biological activity in a cell. Target fusion polypeptides may be useful therapeutically for the treatment of disorders caused by, for example, (i) aberrant modification or mutation of a gene encoding a target polypeptide; (ii) mis-regulation of the gene encoding the target polypeptide; and (iii) aberrant post-translational modification of a target polypeptide. Also, target polypeptides can be used as immunogens to produce anti-target antibodies in a subject, to purify target polypeptide ligands or binding partners, and in screening assays to identify molecules which inhibit or enhance the interaction of a target polypeptide with a substrate.

[0080] In addition, polypeptides can be chemically synthesized using techniques known in the art (See, *e.g.*, Creighton, 1983 *Proteins*. New York, N.Y.: W. H. Freeman and Company; and Hunkapiller et al., (1984) *Nature* July 12 -18;310(5973):105-11). For example, a relative short fragment can be synthesized by use of a peptide synthesizer. Furthermore, if desired, non-classical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the fragment sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ -Abu, ϵ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoroamino acids, designer amino acids such as β -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0081] Polypeptides and polypeptide fragments sometimes are differentially modified during or after translation, *e.g.*, by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH₄; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; and the like. Additional post-translational modifications include, for example, N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of prokaryotic host cell expression. The polypeptide fragments may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the polypeptide.

[0082] Also provided are chemically modified derivatives of polypeptides that can provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (*see e.g.*, U.S. Pat. No: 4,179,337. The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides

may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0083] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (*e.g.*, the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog).

[0084] The polymers should be attached to the polypeptide with consideration of effects on functional or antigenic domains of the polypeptide. There are a number of attachment methods available to those skilled in the art (*e.g.*, EP 0 401 384 (coupling PEG to G-CSF) and Malik et al. (1992) *Exp Hematol.* September;20(8):1028-35 (pegylation of GM-CSF using tresyl chloride)). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues, glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. For therapeutic purposes, the attachment sometimes is at an amino group, such as attachment at the N-terminus or lysine group.

[0085] Proteins can be chemically modified at the N-terminus. Using polyethylene glycol as an illustration of such a composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, and the like), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (*i.e.*, separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus may be accomplished by reductive alkylation, which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

Substantially Identical Nucleic Acids and Polypeptides

[0086] Nucleotide sequences and polypeptide sequences that are substantially identical to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B and the target polypeptide sequences

encoded by those nucleotide sequences, respectively, are included herein. The term “substantially identical” as used herein refers to two or more nucleic acids or polypeptides sharing one or more identical nucleotide sequences or polypeptide sequences, respectively. Included are nucleotide sequences or polypeptide sequences that are 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more (each often within a 1%, 2%, 3% or 4% variability) identical to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence, or other nucleotide sequence referenced in Table B, or the encoded target polypeptide amino acid sequences. One test for determining whether two nucleic acids are substantially identical is to determine the percent of identical nucleotide sequences or polypeptide sequences shared between the nucleic acids or polypeptides.

[0087] Calculations of sequence identity are often performed as follows. Sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). The length of a reference sequence aligned for comparison purposes is sometimes 30% or more, 40% or more, 50% or more, often 60% or more, and more often 70% or more, 80% or more, 90% or more, or 100% of the length of the reference sequence. The nucleotides or amino acids at corresponding nucleotide or polypeptide positions, respectively, are then compared among the two sequences. When a position in the first sequence is occupied by the same nucleotide or amino acid as the corresponding position in the second sequence, the nucleotides or amino acids are deemed to be identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, introduced for optimal alignment of the two sequences.

[0088] Comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. Percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of Meyers & Miller, *CABIOS* 4: 11-17 (1989), which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. Also, percent identity between two amino acid sequences can be determined using the Needleman & Wunsch, *J. Mol. Biol.* 48: 444-453 (1970) algorithm which has been incorporated into the GAP program in the GCG software package (available at the [http](http://www.gcg.com) address www.gcg.com), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. Percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package (available at [http](http://www.gcg.com) address www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A set of parameters often used is a Blossum 62 scoring matrix with a gap open penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

[0089] Another manner for determining if two nucleic acids are substantially identical is to assess whether a polynucleotide homologous to one nucleic acid will hybridize to the other nucleic acid under

stringent conditions. As used herein, the term “stringent conditions” refers to conditions for hybridization and washing. Stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y., 6.3.1-6.3.6 (1989). Aqueous and non-aqueous methods are described in that reference and either can be used. An example of stringent hybridization conditions is hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50°C. Another example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 55°C. A further example of stringent hybridization conditions is hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 60°C. Often, stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C. More often, stringency conditions are 0.5M sodium phosphate, 7% SDS at 65°C, followed by one or more washes at 0.2X SSC, 1% SDS at 65°C.

[0090] An example of a substantially identical nucleotide sequence to a nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B is one that has a different nucleotide sequence but still encodes the same polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B. Another example is a nucleotide sequence that encodes a polypeptide having a polypeptide sequence that is more than 70% or more identical to, sometimes more than 75% or more, 80% or more, or 85% or more identical to, and often more than 90% or more and 95% or more identical to a polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B.

[0091] Nucleotide sequences in SEQ ID NO: 1-13 or referenced in Table B and amino acid sequences of encoded polypeptides can be used as “query sequences” to perform a search against public databases to identify other family members or related sequences, for example. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul *et al.*, *J. Mol. Biol.* 215: 403-10 (1990). BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to nucleotide sequences in SEQ ID NO: 1-13, SEQ ID NO: 14-36 or referenced in Table B. BLAST polypeptide searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to polypeptides encoded by the nucleotide sequences of SEQ ID NO: 14-36 or referenced in Table B. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, *Nucleic Acids Res.* 25(17): 3389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used (*see* the http address www.ncbi.nlm.nih.gov).

[0092] A nucleic acid that is substantially identical to a nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B may include polymorphic sites at positions equivalent to those described herein when the sequences are aligned. For example, using the alignment procedures described herein, SNPs

in a sequence substantially identical to a sequence in SEQ ID NO: 1-13 or referenced in Table B can be identified at nucleotide positions that match (*i.e.*, align) with nucleotides at SNP positions in each nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B. Also, where a polymorphic variation results in an insertion or deletion, insertion or deletion of a nucleotide sequence from a reference sequence can change the relative positions of other polymorphic sites in the nucleotide sequence.

[0093] Substantially identical nucleotide and polypeptide sequences include those that are naturally occurring, such as allelic variants (same locus), splice variants, homologs (different locus), and orthologs (different organism) or can be non-naturally occurring. Non-naturally occurring variants can be generated by mutagenesis techniques, including those applied to polynucleotides, cells, or organisms. The variants can contain nucleotide substitutions, deletions, inversions and insertions. Variation can occur in either or both the coding and non-coding regions. The variations can produce both conservative and non-conservative amino acid substitutions (as compared in the encoded product). Orthologs, homologs, allelic variants, and splice variants can be identified using methods known in the art. These variants normally comprise a nucleotide sequence encoding a polypeptide that is 50% or more, about 55% or more, often about 70-75% or more or about 80-85% or more, and sometimes about 90-95% or more identical to the amino acid sequences of target polypeptides or a fragment thereof. Such nucleic acid molecules can readily be identified as being able to hybridize under stringent conditions to a nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B or a fragment of this sequence. Nucleic acid molecules corresponding to orthologs, homologs, and allelic variants of a nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B can further be identified by mapping the sequence to the same chromosome or locus as the nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B.

[0094] Also, substantially identical nucleotide sequences may include codons that are altered with respect to the naturally occurring sequence for enhancing expression of a target polypeptide in a particular expression system. For example, the nucleic acid can be one in which one or more codons are altered, and often 10% or more or 20% or more of the codons are altered for optimized expression in bacteria (*e.g.*, *E. coli.*), yeast (*e.g.*, *S. cerevisiae*), human (*e.g.*, 293 cells), insect, or rodent (*e.g.*, hamster) cells.

Methods for Identifying Risk of Osteoarthritis

[0095] Methods for prognosing and diagnosing osteoarthritis are included herein. These methods include detecting the presence or absence of one or more polymorphic variations in a nucleotide sequence associated with osteoarthritis, such as variants in or around the loci set forth herein, or a substantially identical sequence thereof, in a sample from a subject, where the presence of a polymorphic variant described herein is indicative of a risk of osteoarthritis. Determining a risk of osteoarthritis sometimes refers to determining whether an individual is at an increased risk of osteoarthritis (*e.g.*, intermediate risk or higher risk).

[0096] Thus, featured herein is a method for identifying a subject who is at risk of osteoarthritis, which comprises detecting an aberration associated with osteoarthritis in a nucleic acid sample from the subject. An embodiment is a method for detecting a risk of osteoarthritis in a subject, which comprises detecting the presence or absence of a polymorphic variation associated with osteoarthritis at a polymorphic site in a nucleotide sequence in a nucleic acid sample from a subject, where the nucleotide sequence comprises a polynucleotide sequence selected from the group consisting of: (a) a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; (b) a nucleotide sequence which encodes a polypeptide consisting of an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; (c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B, or a nucleotide sequence about 90% or more identical to a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; and (d) a fragment of a nucleotide sequence of (a), (b), or (c) comprising the polymorphic site; whereby the presence of the polymorphic variation is indicative of a predisposition to osteoarthritis in the subject. In certain embodiments, polymorphic variants at the positions described herein are detected for determining a risk of osteoarthritis, and polymorphic variants at positions in linkage disequilibrium with these positions are detected for determining a risk of osteoarthritis. As used herein, the terms "SEQ ID NO: 1-13" and other nucleotide sequences "referenced in Table B" refers to individual sequences in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 or any individual sequence referenced in Table B, or any individual nucleic acid sequence provided in the sequence listing, including SEQ ID NO: 14-36 each sequence being separately applicable to embodiments described herein.

[0097] Risk of osteoarthritis sometimes is expressed as a probability, such as an odds ratio, percentage, or risk factor. Risk often is based upon the presence or absence of one or more polymorphic variants described herein, and also may be based in part upon phenotypic traits of the individual being tested. Methods for calculating risk based upon patient data are well known (*see, e.g., Agresti, Categorical Data Analysis*, 2nd Ed. 2002. Wiley). Allelotyping and genotyping analyses may be carried out in populations other than those exemplified herein to enhance the predictive power of the prognostic method. These further analyses are executed in view of the exemplified procedures described herein, and may be based upon the same polymorphic variations or additional polymorphic variations.

[0098] In certain embodiments, determining the presence of a combination of two or more polymorphic variants associated with osteoarthritis in one or more genetic loci (*e.g., one or more genes*) of the sample is determined to identify, quantify and/or estimate, risk of osteoarthritis. The risk often is the probability of having or developing osteoarthritis. The risk sometimes is expressed as a relative risk with respect to a population average risk of osteoarthritis, and sometimes is expressed as a relative risk with respect to the lowest risk group. Such relative risk assessments often are based upon penetrance values determined by statistical methods, and are particularly useful to clinicians and insurance companies for assessing risk of osteoarthritis (*e.g., a clinician can target appropriate detection,*

prevention and therapeutic regimens to a patient after determining the patient's risk of osteoarthritis, and an insurance company can fine tune actuarial tables based upon population genotype assessments of osteoarthritis risk). Risk of osteoarthritis sometimes is expressed as an odds ratio, which is the odds of a particular person having a genotype has or will develop osteoarthritis with respect to another genotype group (*e.g.*, the most disease protective genotype or population average). In related embodiments, the determination is utilized to identify a subject at risk of osteoarthritis. In an embodiment, two or more polymorphic variations are detected in two or more regions in human genomic DNA associated with increased risk of osteoarthritis, such as a locus containing a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* or other locus referenced in Table B, for example. In certain embodiments, 3 or more, or 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 80, 90, 100 or more polymorphic variants are detected in the sample. In specific embodiments, polymorphic variants are detected in a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* region or other region referenced in Table B, for example. In another embodiment, polymorphic variants are detected at two or three positions in a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B. In certain embodiments, polymorphic variants are detected at other genetic loci (*e.g.*, the polymorphic variants can be detected in a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B in addition to other loci or only in other loci), where the other loci include but are not limited to those described in patent applications 60/559,011; 60/559,202; 60/559,203; 60/559,042; 60/559,275; 60/559,040 and 60/559,225, each of which is entitled "Methods for Identifying Risk of Osteoarthritis and Treatments Thereof," each of which was filed on 1 April 2004 and each of which is incorporated herein by reference in its entirety in jurisdictions allowing incorporation by reference.

[0099] Results from prognostic tests may be combined with other test results to diagnose osteoarthritis. For example, prognostic results may be gathered, a patient sample may be ordered based on a determined predisposition to osteoarthritis, the patient sample is analyzed, and the results of the analysis may be utilized to diagnose osteoarthritis. Also osteoarthritis diagnostic method can be developed from studies used to generate prognostic methods in which populations are stratified into subpopulations having different progressions of osteoarthritis. In another embodiment, prognostic results may be gathered, a patient's risk factors for developing osteoarthritis (*e.g.*, age, weight, occupational history, race, diet) analyzed, and a patient sample may be ordered based on a determined predisposition to osteoarthritis.

[0100] The nucleic acid sample typically is isolated from a biological sample obtained from a subject. For example, nucleic acid can be isolated from blood, saliva, sputum, urine, cell scrapings, and biopsy tissue. The nucleic acid sample can be isolated from a biological sample using standard techniques, such as the technique described in Example 2. As used herein, the term "subject" refers primarily to humans but also refers to other mammals such as dogs, cats, and ungulates (*e.g.*, cattle, sheep, and swine). Subjects also include avians (*e.g.*, chickens and turkeys), reptiles, and fish (*e.g.*,

salmon), as embodiments described herein can be adapted to nucleic acid samples isolated from any of these organisms. The nucleic acid sample may be isolated from the subject and then directly utilized in a method for determining the presence of a polymorphic variant, or alternatively, the sample may be isolated and then stored (*e.g.*, frozen) for a period of time before being subjected to analysis.

[0101] The presence or absence of a polymorphic variant is determined using one or both chromosomal complements represented in the nucleic acid sample. Determining the presence or absence of a polymorphic variant in both chromosomal complements represented in a nucleic acid sample from a subject having a copy of each chromosome is useful for determining the zygosity of an individual for the polymorphic variant (*i.e.*, whether the individual is homozygous or heterozygous for the polymorphic variant). Any oligonucleotide-based diagnostic may be utilized to determine whether a sample includes the presence or absence of a polymorphic variant in a sample. For example, primer extension methods, ligase sequence determination methods (*e.g.*, U.S. Pat. Nos. 5,679,524 and 5,952,174, and WO 01/27326), mismatch sequence determination methods (*e.g.*, U.S. Pat. Nos. 5,851,770; 5,958,692; 6,110,684; and 6,183,958), microarray sequence determination methods, restriction fragment length polymorphism (RFLP), single strand conformation polymorphism detection (SSCP) (*e.g.*, U.S. Pat. Nos. 5,891,625 and 6,013,499), PCR-based assays (*e.g.*, TAQMAN® PCR System (Applied Biosystems)), and nucleotide sequencing methods may be used.

[0102] Oligonucleotide extension methods typically involve providing a pair of oligonucleotide primers in a polymerase chain reaction (PCR) or in other nucleic acid amplification methods for the purpose of amplifying a region from the nucleic acid sample that comprises the polymorphic variation. One oligonucleotide primer is complementary to a region 3' of the polymorphism and the other is complementary to a region 5' of the polymorphism. A PCR primer pair may be used in methods disclosed in U.S. Pat. Nos. 4,683,195; 4,683,202, 4,965,188; 5,656,493; 5,998,143; 6,140,054; WO 01/27327; and WO 01/27329 for example. PCR primer pairs may also be used in any commercially available machines that perform PCR, such as any of the GENEAMP® Systems available from Applied Biosystems. Also, those of ordinary skill in the art will be able to design oligonucleotide primers based upon a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B using knowledge available in the art.

[0103] Also provided is an extension oligonucleotide that hybridizes to the amplified fragment adjacent to the polymorphic variation. As used herein, the term "adjacent" refers to the 3' end of the extension oligonucleotide being often 1 nucleotide from the 5' end of the polymorphic site, and sometimes 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides from the 5' end of the polymorphic site, in the nucleic acid when the extension oligonucleotide is hybridized to the nucleic acid. The extension oligonucleotide then is extended by one or more nucleotides, and the number and/or type of nucleotides that are added to the extension oligonucleotide determine whether the polymorphic variant is present. Oligonucleotide extension methods are disclosed, for example, in U.S. Pat. Nos. 4,656,127; 4,851,331; 5,679,524; 5,834,189; 5,876,934; 5,908,755; 5,912,118; 5,976,802; 5,981,186; 6,004,744; 6,013,431;

6,017,702; 6,046,005; 6,087,095; 6,210,891; and WO 01/20039. Oligonucleotide extension methods using mass spectrometry are described, for example, in U.S. Pat. Nos. 5,547,835; 5,605,798; 5,691,141; 5,849,542; 5,869,242; 5,928,906; 6,043,031; and 6,194,144, and a method often utilized is described herein in Example 2.

[0104] A microarray can be utilized for determining whether a polymorphic variant is present or absent in a nucleic acid sample. A microarray may include any oligonucleotides described herein, and methods for making and using oligonucleotide microarrays suitable for diagnostic use are disclosed in U.S. Pat. Nos. 5,492,806; 5,525,464; 5,589,330; 5,695,940; 5,849,483; 6,018,041; 6,045,996; 6,136,541; 6,142,681; 6,156,501; 6,197,506; 6,223,127; 6,225,625; 6,229,911; 6,239,273; WO 00/52625; WO 01/25485; and WO 01/29259. The microarray typically comprises a solid support and the oligonucleotides may be linked to this solid support by covalent bonds or by non-covalent interactions. The oligonucleotides may also be linked to the solid support directly or by a spacer molecule. A microarray may comprise one or more oligonucleotides complementary to a polymorphic site set forth herein.

[0105] A kit also may be utilized for determining whether a polymorphic variant is present or absent in a nucleic acid sample. A kit often comprises one or more pairs of oligonucleotide primers useful for amplifying a fragment of a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B or a substantially identical sequence thereof, where the fragment includes a polymorphic site. The kit sometimes comprises a polymerizing agent, for example, a thermostable nucleic acid polymerase such as one disclosed in U.S. Pat. Nos. 4,889,818 or 6,077,664. Also, the kit often comprises an elongation oligonucleotide that hybridizes to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B in a nucleic acid sample adjacent to the polymorphic site. Where the kit includes an elongation oligonucleotide, it also often comprises chain elongating nucleotides, such as dATP, dTTP, dGTP, dCTP, and dITP, including analogs of dATP, dTTP, dGTP, dCTP and dITP, provided that such analogs are substrates for a thermostable nucleic acid polymerase and can be incorporated into a nucleic acid chain elongated from the extension oligonucleotide. Along with chain elongating nucleotides would be one or more chain terminating nucleotides such as ddATP, ddTTP, ddGTP, ddCTP, and the like. In an embodiment, the kit comprises one or more oligonucleotide primer pairs, a polymerizing agent, chain elongating nucleotides, at least one elongation oligonucleotide, and one or more chain terminating nucleotides. Kits optionally include buffers, vials, microtiter plates, and instructions for use.

[0106] An individual identified as being at risk of osteoarthritis may be heterozygous or homozygous with respect to the allele associated with a higher risk of osteoarthritis. A subject homozygous for an allele associated with an increased risk of osteoarthritis is at a comparatively high risk of osteoarthritis, a subject heterozygous for an allele associated with an increased risk of osteoarthritis is at a comparatively intermediate risk of osteoarthritis, and a subject homozygous for an allele associated with a decreased risk of osteoarthritis is at a comparatively low risk of osteoarthritis. A

genotype may be assessed for a complementary strand, such that the complementary nucleotide at a particular position is detected.

[0107] Also featured are methods for determining risk of osteoarthritis and/or identifying a subject at risk of osteoarthritis by contacting a polypeptide or protein encoded by a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B from a subject with an antibody that specifically binds to an epitope associated with increased risk of osteoarthritis in the polypeptide (e.g., an epitope comprising a valine at position 245 in an *IL1RL1* polypeptide).

Applications of Prognostic and Diagnostic Results to Pharmacogenomic Methods

[0108] Pharmacogenomics is a discipline that involves tailoring a treatment for a subject according to the subject's genotype as a particular treatment regimen may exert a differential effect depending upon the subject's genotype. For example, based upon the outcome of a prognostic test described herein, a clinician or physician may target pertinent information and preventative or therapeutic treatments to a subject who would be benefited by the information or treatment and avoid directing such information and treatments to a subject who would not be benefited (e.g., the treatment has no therapeutic effect and/or the subject experiences adverse side effects).

[0109] The following is an example of a pharmacogenomic embodiment. A particular treatment regimen can exert a differential effect depending upon the subject's genotype. Where a candidate therapeutic exhibits a significant interaction with a major allele and a comparatively weak interaction with a minor allele (e.g., an order of magnitude or greater difference in the interaction), such a therapeutic typically would not be administered to a subject genotyped as being homozygous for the minor allele, and sometimes not administered to a subject genotyped as being heterozygous for the minor allele. In another example, where a candidate therapeutic is not significantly toxic when administered to subjects who are homozygous for a major allele but is comparatively toxic when administered to subjects heterozygous or homozygous for a minor allele, the candidate therapeutic is not typically administered to subjects who are genotyped as being heterozygous or homozygous with respect to the minor allele.

[0110] The methods described herein are applicable to pharmacogenomic methods for preventing, alleviating or treating osteoarthritis. For example, a nucleic acid sample from an individual may be subjected to a prognostic test described herein. Where one or more polymorphic variations associated with increased risk of osteoarthritis are identified in a subject, information for preventing or treating osteoarthritis and/or one or more osteoarthritis treatment regimens then may be prescribed to that subject.

[0111] In certain embodiments, a treatment or preventative regimen is specifically prescribed and/or administered to individuals who will most benefit from it based upon their risk of developing osteoarthritis assessed by the methods described herein. Thus, provided are methods for identifying a subject predisposed to osteoarthritis and then prescribing a therapeutic or preventative regimen to

individuals identified as having a predisposition. Thus, certain embodiments are directed to a method for reducing osteoarthritis in a subject, which comprises: detecting the presence or absence of a polymorphic variant associated with osteoarthritis in a nucleotide sequence in a nucleic acid sample from a subject, where the nucleotide sequence comprises a polynucleotide sequence selected from the group consisting of: (a) a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; (b) a nucleotide sequence which encodes a polypeptide consisting of an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; (c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B, or a nucleotide sequence about 90% or more identical to a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; and (d) a fragment of a polynucleotide sequence of (a), (b), or (c); and prescribing or administering a treatment regimen to a subject from whom the sample originated where the presence of a polymorphic variation associated with osteoarthritis is detected in the nucleotide sequence. In these methods, predisposition results may be utilized in combination with other test results to diagnose osteoarthritis.

[0112] Certain preventative treatments often are prescribed to subjects having a predisposition to osteoarthritis and where the subject is diagnosed with osteoarthritis or is diagnosed as having symptoms indicative of an early stage of osteoarthritis. The treatment sometimes is preventative (*e.g.*, is prescribed or administered to reduce the probability that osteoarthritis arises or progresses), sometimes is therapeutic, and sometimes delays, alleviates or halts the progression of osteoarthritis. Any known preventative or therapeutic treatment for alleviating or preventing the occurrence of osteoarthritis is prescribed and/or administered. For example, the treatment often is directed to decreasing pain and improving joint movement. Examples of OA treatments include exercises to keep joints flexible and improve muscle strength. Different medications to control pain, including corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs, *e.g.*, Voltaren); cyclooxygenase-2 (COX-2) inhibitors (*e.g.*, Celebrex, Vioxx, Mobic, and Bextra); monoclonal antibodies (*e.g.*, Remicade); tumor necrosis factor inhibitors (*e.g.*, Enbrel); or injections of glucocorticoids, hyaluronic acid or chondroitin sulfate into joints that are inflamed and not responsive to NSAIDs. Orally administered chondroitin sulfate also may be used as a therapeutic, as it may increase hyaluronic acid levels and viscosity of synovial fluid, and decrease collagenase levels in synovial fluid. Also, glucosamine can serve as an OA therapeutic as delivering it into joints may inhibit enzymes involved in cartilage degradation and enhance the production of hyaluronic acid. For mild pain without inflammation, acetaminophen may be used. Other treatments include: heat/cold therapy for temporary pain relief; joint protection to prevent strain or stress on painful joints; surgery to relieve chronic pain in damaged joints; and weight control to prevent extra stress on weight-bearing joints.

[0113] As therapeutic approaches for treating osteoarthritis continue to evolve and improve, the goal of treatments for osteoarthritis related disorders is to intervene even before clinical signs first manifest. Thus, genetic markers associated with susceptibility to osteoarthritis prove useful for early diagnosis, prevention and treatment of osteoarthritis.

[0114] As osteoarthritis preventative and treatment information can be specifically targeted to subjects in need thereof (e.g., those at risk of developing osteoarthritis or those in an early stage of osteoarthritis), provided herein is a method for preventing or reducing the risk of developing osteoarthritis in a subject, which comprises: (a) detecting the presence or absence of a polymorphic variation associated with osteoarthritis at a polymorphic site in a nucleotide sequence in a nucleic acid sample from a subject; (b) identifying a subject with a predisposition to osteoarthritis, whereby the presence of the polymorphic variation is indicative of a predisposition to osteoarthritis in the subject; and (c) if such a predisposition is identified, providing the subject with information about methods or products to prevent or reduce osteoarthritis or to delay the onset of osteoarthritis. Also provided is a method of targeting information or advertising to a subpopulation of a human population based on the subpopulation being genetically predisposed to a disease or condition, which comprises: (a) detecting the presence or absence of a polymorphic variation associated with osteoarthritis at a polymorphic site in a nucleotide sequence in a nucleic acid sample from a subject; (b) identifying the subpopulation of subjects in which the polymorphic variation is associated with osteoarthritis; and (c) providing information only to the subpopulation of subjects about a particular product which may be obtained and consumed or applied by the subject to help prevent or delay onset of the disease or condition.

[0115] Pharmacogenomics methods also may be used to analyze and predict a response to osteoarthritis treatment or a drug. For example, if pharmacogenomics analysis indicates a likelihood that an individual will respond positively to osteoarthritis treatment with a particular drug, the drug may be administered to the individual. Conversely, if the analysis indicates that an individual is likely to respond negatively to treatment with a particular drug, an alternative course of treatment may be prescribed. A negative response may be defined as either the absence of an efficacious response or the presence of toxic side effects. The response to a therapeutic treatment can be predicted in a background study in which subjects in any of the following populations are genotyped: a population that responds favorably to a treatment regimen, a population that does not respond significantly to a treatment regimen, and a population that responds adversely to a treatment regimen (e.g., exhibits one or more side effects). These populations are provided as examples and other populations and subpopulations may be analyzed. Based upon the results of these analyses, a subject is genotyped to predict whether he or she will respond favorably to a treatment regimen, not respond significantly to a treatment regimen, or respond adversely to a treatment regimen.

[0116] The tests described herein also are applicable to clinical drug trials. One or more polymorphic variants indicative of response to an agent for treating osteoarthritis or to side effects to an agent for treating osteoarthritis may be identified using the methods described herein. Thereafter, potential participants in clinical trials of such an agent may be screened to identify those individuals most likely to respond favorably to the drug and exclude those likely to experience side effects. In that way, the effectiveness of drug treatment may be measured in individuals who respond positively to the drug, without lowering the measurement as a result of the inclusion of individuals who are unlikely to respond positively in the study and without risking undesirable safety problems.

[0117] Thus, another embodiment is a method of selecting an individual for inclusion in a clinical trial of a treatment or drug comprising the steps of: (a) obtaining a nucleic acid sample from an individual; (b) determining the identity of a polymorphic variation which is associated with a positive response to the treatment or the drug, or at least one polymorphic variation which is associated with a negative response to the treatment or the drug in the nucleic acid sample, and (c) including the individual in the clinical trial if the nucleic acid sample contains said polymorphic variation associated with a positive response to the treatment or the drug or if the nucleic acid sample lacks said polymorphic variation associated with a negative response to the treatment or the drug. In addition, the methods described herein for selecting an individual for inclusion in a clinical trial of a treatment or drug encompass methods with any further limitation described in this disclosure, or those following, specified alone or in any combination. The polymorphic variation may be in a sequence selected individually or in any combination from the group consisting of (i) a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; (ii) a nucleotide sequence which encodes a polypeptide consisting of an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; (iii) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B, or a nucleotide sequence about 90% or more identical to a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B; and (iv) a fragment of a polynucleotide sequence of (i), (ii), or (iii) comprising the polymorphic site. The including step (c) optionally comprises administering the drug or the treatment to the individual if the nucleic acid sample contains the polymorphic variation associated with a positive response to the treatment or the drug and the nucleic acid sample lacks said biallelic marker associated with a negative response to the treatment or the drug.

[0118] Also provided herein is a method of partnering between a diagnostic/prognostic testing provider and a provider of a consumable product, which comprises: (a) the diagnostic/prognostic testing provider detects the presence or absence of a polymorphic variation associated with osteoarthritis at a polymorphic site in a nucleotide sequence in a nucleic acid sample from a subject; (b) the diagnostic/prognostic testing provider identifies the subpopulation of subjects in which the polymorphic variation is associated with osteoarthritis; (c) the diagnostic/prognostic testing provider forwards information to the subpopulation of subjects about a particular product which may be obtained and consumed or applied by the subject to help prevent or delay onset of the disease or condition; and (d) the provider of a consumable product forwards to the diagnostic test provider a fee every time the diagnostic/prognostic test provider forwards information to the subject as set forth in step (c) above.

Compositions Comprising Osteoarthritis-Directed Molecules

[0119] Featured herein is a composition comprising a cell from a subject having osteoarthritis or at risk of osteoarthritis and one or more molecules specifically directed and targeted to a nucleic acid comprising a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence, other nucleotide sequence referenced in Table B, or an encoded amino

acid sequence referenced herein. Such directed molecules include, but are not limited to, a compound that binds to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence, or other nucleotide sequence referenced in Table B, or encoded amino acid sequence; a RNAi or siRNA molecule having a strand complementary or substantially complementary to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B (e.g., hybridizes to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B under conditions of high stringency); an antisense nucleic acid complementary or substantially complementary to an RNA encoded by a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B (e.g., hybridizes to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B under conditions of high stringency); a ribozyme that hybridizes to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B (e.g., hybridizes to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B under conditions of high stringency); a nucleic acid aptamer that specifically binds a polypeptide encoded by a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B; and an antibody that specifically binds to a polypeptide encoded by a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B or binds to a nucleic acid having such a nucleotide sequence. In an embodiment, the antibody selectively binds to an epitope comprising an amino acid encoded by rs1367117, rs1041973 and rs398829. In specific embodiments, the osteoarthritis directed molecule interacts with a nucleic acid or polypeptide variant associated with osteoarthritis, such as variants referenced herein. In other embodiments, the osteoarthritis directed molecule interacts with a polypeptide involved in a signal pathway of a polypeptide encoded by a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B, or a nucleic acid comprising such a nucleotide sequence.

[0120] Compositions sometimes include an adjuvant known to stimulate an immune response, and in certain embodiments, an adjuvant that stimulates a T-cell lymphocyte response. Adjuvants are known, including but not limited to an aluminum adjuvant (e.g., aluminum hydroxide); a cytokine adjuvant or adjuvant that stimulates a cytokine response (e.g., interleukin (IL)-12 and/or gamma-interferon cytokines); a Freund-type mineral oil adjuvant emulsion (e.g., Freund's complete or incomplete adjuvant); a synthetic lipoid compound; a copolymer adjuvant (e.g., TitreMax); a saponin; Quil A; a liposome; an oil-in-water emulsion (e.g., an emulsion stabilized by Tween 80 and pluronic

polyoxyethylene/polyoxypropylene block copolymer (Syntex Adjuvant Formulation); TitreMax; detoxified endotoxin (MPL) and mycobacterial cell wall components (TDW, CWS) in 2% squalene (Ribi Adjuvant System)); a muramyl dipeptide; an immune-stimulating complex (ISCOM, *e.g.*, an Ag-modified saponin/cholesterol micelle that forms stable cage-like structure); an aqueous phase adjuvant that does not have a depot effect (*e.g.*, Gerbu adjuvant); a carbohydrate polymer (*e.g.*, AdjuPrime); L-tyrosine; a manide-oleate compound (*e.g.*, Montanide); an ethylene-vinyl acetate copolymer (*e.g.*, Elvax 40W1,2); or lipid A, for example. Such compositions are useful for generating an immune response against osteoarthritis directed molecule (*e.g.*, an HLA-binding subsequence within a polypeptide encoded by a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence). In such methods, a peptide having an amino acid subsequence of a polypeptide encoded by a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence is delivered to a subject, where the subsequence binds to an HLA molecule and induces a CTL lymphocyte response. The peptide sometimes is delivered to the subject as an isolated peptide or as a minigene in a plasmid that encodes the peptide. Methods for identifying HLA-binding subsequences in such polypeptides are known (see *e.g.*, publication WO02/20616 and PCT application US98/01373 for methods of identifying such sequences).

[0121] The cell may be in a group of cells cultured *in vitro* or in a tissue maintained *in vitro* or present in an animal *in vivo* (*e.g.*, a rat, mouse, ape or human). In certain embodiments, a composition comprises a component from a cell such as a nucleic acid molecule (*e.g.*, genomic DNA), a protein mixture or isolated protein, for example. The aforementioned compositions have utility in diagnostic, prognostic and pharmacogenomic methods described previously and in therapeutics described hereafter. Certain osteoarthritis directed molecules are described in greater detail below.

Compounds

[0122] Compounds can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive (see, *e.g.*, Zuckermann et al., J. Med. Chem. 37: 2678-85 (1994)); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; "one-bead one-compound" library methods; and synthetic library methods using affinity chromatography selection. Biological library and peptoid library approaches are typically limited to peptide libraries, while the other approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, Anticancer Drug Des. 12: 145, (1997)). Examples of methods for synthesizing molecular libraries are described, for example, in DeWitt et al., Proc. Natl. Acad. Sci. U.S.A. 90: 6909 (1993); Erb et al., Proc. Natl. Acad. Sci. USA 91: 11422 (1994); Zuckermann et al., J. Med. Chem. 37: 2678 (1994); Cho et al., Science 261: 1303 (1993); Carrell et al., Angew. Chem. Int. Ed. Engl. 33: 2059 (1994); Carrell et al., Angew. Chem. Int. Ed. Engl. 33: 2061 (1994); and in Gallop et al., J. Med. Chem. 37: 1233 (1994).

[0123] Libraries of compounds may be presented in solution (*e.g.*, Houghten, *Biotechniques* 13: 412-421 (1992)), or on beads (Lam, *Nature* 354: 82-84 (1991)), chips (Fodor, *Nature* 364: 555-556 (1993)), bacteria or spores (Ladner, United States Patent No. 5,223,409), plasmids (Cull et al., *Proc. Natl. Acad. Sci. USA* 89: 1865-1869 (1992)) or on phage (Scott and Smith, *Science* 249: 386-390 (1990); Devlin, *Science* 249: 404-406 (1990); Cwirla et al., *Proc. Natl. Acad. Sci.* 87: 6378-6382 (1990); Felici, *J. Mol. Biol.* 222: 301-310 (1991); Ladner *supra.*).

[0124] A compound sometimes alters expression and sometimes alters activity of a polypeptide target and may be a small molecule. Small molecules include, but are not limited to, peptides, peptidomimetics (*e.g.*, peptoids), amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (*i.e.*, including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds.

Antisense Nucleic Acid Molecules, Ribozymes, RNAi, siRNA and Modified Nucleic Acid Molecules

[0125] An “antisense” nucleic acid refers to a nucleotide sequence complementary to a “sense” nucleic acid encoding a polypeptide, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. The antisense nucleic acid can be complementary to an entire coding strand, or to a portion thereof or a substantially identical sequence thereof. In another embodiment, the antisense nucleic acid molecule is antisense to a “noncoding region” of the coding strand of a nucleotide sequence (*e.g.*, 5' and 3' untranslated regions in SEQ ID NO: 1-13 or a nucleotide sequence referenced in Table B).

[0126] An antisense nucleic acid can be designed such that it is complementary to the entire coding region of an mRNA encoded by a nucleotide sequence (*e.g.*, SEQ ID NO: 1-13, SEQ ID NO: 14-36 or a nucleotide sequence referenced in Table B), and often the antisense nucleic acid is an oligonucleotide antisense to only a portion of a coding or noncoding region of the mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of the mRNA, *e.g.*, between the -10 and +10 regions of the target gene nucleotide sequence of interest. An antisense oligonucleotide can be, for example, about 7, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, or more nucleotides in length. The antisense nucleic acids, which include the ribozymes described hereafter, can be designed to target a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPI*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXLI*, *CASPR4* or *APOL3* nucleotide sequence, often a variant associated with osteoarthritis, or a substantially identical sequence thereof. Among the variants, minor alleles and major alleles can be targeted, and those associated with a higher risk of osteoarthritis are often designed, tested, and administered to subjects.

[0127] An antisense nucleic acid can be constructed using chemical synthesis and enzymatic ligation reactions using standard procedures. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Antisense nucleic acid also can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

[0128] When utilized as therapeutics, antisense nucleic acids typically are administered to a subject (e.g., by direct injection at a tissue site) or generated in situ such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a polypeptide and thereby inhibit expression of the polypeptide, for example, by inhibiting transcription and/or translation. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then are administered systemically. For systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, for example, by linking antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. Antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. Sufficient intracellular concentrations of antisense molecules are achieved by incorporating a strong promoter, such as a pol II or pol III promoter, in the vector construct.

[0129] Antisense nucleic acid molecules sometimes are alpha-anomeric nucleic acid molecules. An alpha-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual beta-units, the strands run parallel to each other (Gaultier et al., Nucleic Acids. Res. 15: 6625-6641 (1987)). Antisense nucleic acid molecules can also comprise a 2'-O-methylribonucleotide (Inoue et al., Nucleic Acids Res. 15: 6131-6148 (1987)) or a chimeric RNA-DNA analogue (Inoue et al., FEBS Lett. 215: 327-330 (1987)). Antisense nucleic acids sometimes are composed of DNA or PNA or any other nucleic acid derivatives described previously.

[0130] In another embodiment, an antisense nucleic acid is a ribozyme. A ribozyme having specificity for a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B can include one or more sequences complementary to such a nucleotide sequence, and a sequence having a known catalytic region responsible for mRNA cleavage (see e.g., U.S. Pat. No. 5,093,246 or Haselhoff and Gerlach, Nature 334: 585-591 (1988)). For example, a derivative of a *Tetrahymena* L-19 IVS RNA is sometimes utilized in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a mRNA (see e.g., Cech et al. U.S. Patent No. 4,987,071; and Cech et al. U.S. Patent No. 5,116,742). Also, target mRNA sequences can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see e.g., Bartel & Szostak, Science 261: 1411-1418 (1993)).

[0131] Osteoarthritis directed molecules include in certain embodiments nucleic acids that can form triple helix structures with a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B, or a substantially identical sequence thereof, especially one that includes a regulatory region that controls expression of a polypeptide. Gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of a nucleotide sequence referenced herein or a substantially identical sequence (e.g., promoter and/or enhancers) to form triple helical structures that prevent transcription of a gene in target cells (see e.g., Helene, *Anticancer Drug Des.* 6(6): 569-84 (1991); Helene et al., *Ann. N.Y. Acad. Sci.* 660: 27-36 (1992); and Maher, *Bioassays* 14(12): 807-15 (1992). Potential sequences that can be targeted for triple helix formation can be increased by creating a so-called "switchback" nucleic acid molecule. Switchback molecules are synthesized in an alternating 5'-3', 3'-5' manner, such that they base pair with first one strand of a duplex and then the other, eliminating the necessity for a sizeable stretch of either purines or pyrimidines to be present on one strand of a duplex.

[0132] Osteoarthritis directed molecules include RNAi and siRNA nucleic acids. Gene expression may be inhibited by the introduction of double-stranded RNA (dsRNA), which induces potent and specific gene silencing, a phenomenon called RNA interference or RNAi. See, e.g., Fire et al., US Patent Number 6,506,559; Tuschl et al. PCT International Publication No. WO 01/75164; Kay et al. PCT International Publication No. WO 03/010180A1; or Bosher JM, Labouesse, *Nat Cell Biol* 2000 Feb;2(2):E31-6. This process has been improved by decreasing the size of the double-stranded RNA to 20-24 base pairs (to create small-interfering RNAs or siRNAs) that "switched off" genes in mammalian cells without initiating an acute phase response, i.e., a host defense mechanism that often results in cell death (see, e.g., Caplen et al. *Proc Natl Acad Sci U S A.* 2001 Aug 14;98(17):9742-7 and Elbashir et al. *Methods* 2002 Feb;26(2):199-213). There is increasing evidence of post-transcriptional gene silencing by RNA interference (RNAi) for inhibiting targeted expression in mammalian cells at the mRNA level, in human cells. There is additional evidence of effective methods for inhibiting the proliferation and migration of tumor cells in human patients, and for inhibiting metastatic cancer development (see, e.g., U.S. Patent Application No. US2001000993183; Caplen et al. *Proc Natl Acad Sci U S A.*; and Abderrahmani et al. *Mol Cell Biol* 2001 Nov21(21):7256-67).

[0133] An "siRNA" or "RNAi" refers to a nucleic acid that forms a double stranded RNA and has the ability to reduce or inhibit expression of a gene or target gene when the siRNA is delivered to or expressed in the same cell as the gene or target gene. "siRNA" refers to short double-stranded RNA formed by the complementary strands. Complementary portions of the siRNA that hybridize to form the double stranded molecule often have substantial or complete identity to the target molecule sequence. In one embodiment, an siRNA refers to a nucleic acid that has substantial or complete identity to a target gene and forms a double stranded siRNA.

[0134] When designing the siRNA molecules, the targeted region often is selected from a given DNA sequence beginning 50 to 100 nucleotides downstream of the start codon. See, e.g., Elbashir et

al., Methods 26:199-213 (2002). Initially, 5' or 3' UTRs and regions nearby the start codon were avoided assuming that UTR-binding proteins and/or translation initiation complexes may interfere with binding of the siRNP or RISC endonuclease complex. Sometimes regions of the target 23 nucleotides in length conforming to the sequence motif AA(N19)TT (N, an nucleotide), and regions with approximately 30% to 70% G/C-content (often about 50% G/C-content) often are selected. If no suitable sequences are found, the search often is extended using the motif NA(N21). The sequence of the sense siRNA sometimes corresponds to (N19) TT or N21 (position 3 to 23 of the 23-nt motif), respectively. In the latter case, the 3' end of the sense siRNA often is converted to TT. The rationale for this sequence conversion is to generate a symmetric duplex with respect to the sequence composition of the sense and antisense 3' overhangs. The antisense siRNA is synthesized as the complement to position 1 to 21 of the 23-nt motif. Because position 1 of the 23-nt motif is not recognized sequence-specifically by the antisense siRNA, the 3'-most nucleotide residue of the antisense siRNA can be chosen deliberately. However, the penultimate nucleotide of the antisense siRNA (complementary to position 2 of the 23-nt motif) often is complementary to the targeted sequence. For simplifying chemical synthesis, TT often is utilized. siRNAs corresponding to the target motif NAR(N17)YNN, where R is purine (A,G) and Y is pyrimidine (C,U), often are selected. Respective 21 nucleotide sense and antisense siRNAs often begin with a purine nucleotide and can also be expressed from a pol III expression vectors without a change in targeting site. Expression of RNAs from pol III promoters often is efficient when the first transcribed nucleotide is a purine.

[0135] The sequence of the siRNA can correspond to the full length target gene, or a subsequence thereof. Often, the siRNA is about 15 to about 50 nucleotides in length (*e.g.*, each complementary sequence of the double stranded siRNA is 15-50 nucleotides in length, and the double stranded siRNA is about 15-50 base pairs in length, sometimes about 20-30 nucleotides in length or about 20-25 nucleotides in length, *e.g.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length). The siRNA sometimes is about 21 nucleotides in length. Methods of using siRNA are well known in the art, and specific siRNA molecules may be purchased from a number of companies including Dharmacon Research, Inc.

[0136] Antisense, ribozyme, RNAi and siRNA nucleic acids can be altered to form modified nucleic acid molecules. The nucleic acids can be altered at base moieties, sugar moieties or phosphate backbone moieties to improve stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of nucleic acid molecules can be modified to generate peptide nucleic acids (see Hyrup et al., Bioorganic & Medicinal Chemistry 4 (1): 5-23 (1996)). As used herein, the terms "peptide nucleic acid" or "PNA" refers to a nucleic acid mimic such as a DNA mimic, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of a PNA can allow for specific hybridization to DNA and RNA under conditions of low ionic strength. Synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described, for example, in Hyrup et al., (1996) supra and Perry-O'Keefe et al., Proc. Natl. Acad. Sci. 93: 14670-675 (1996).

[0137] PNA nucleic acids can be used in prognostic, diagnostic, and therapeutic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNA nucleic acid molecules can also be used in the analysis of single base pair mutations in a gene, (e.g., by PNA-directed PCR clamping); as “artificial restriction enzymes” when used in combination with other enzymes, (e.g., S1 nucleases (Hyrup (1996) supra)); or as probes or primers for DNA sequencing or hybridization (Hyrup et al., (1996) supra; Perry-O’Keefe supra).

[0138] In other embodiments, oligonucleotides may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across cell membranes (see e.g., Letsinger et al., Proc. Natl. Acad. Sci. USA 86: 6553-6556 (1989); Lemaitre et al., Proc. Natl. Acad. Sci. USA 84: 648-652 (1987); PCT Publication No. W088/09810) or the blood-brain barrier (see, e.g., PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (See, e.g., Krol et al., Bio-Techniques 6: 958-976 (1988)) or intercalating agents. (See, e.g., Zon, Pharm. Res. 5: 539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule, (e.g., a peptide, hybridization triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

[0139] Also included herein are molecular beacon oligonucleotide primer and probe molecules having one or more regions complementary to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B, or a substantially identical sequence thereof, two complementary regions one having a fluorophore and one a quencher such that the molecular beacon is useful for quantifying the presence of the nucleic acid in a sample. Molecular beacon nucleic acids are described, for example, in Lizardi et al., U.S. Patent No. 5,854,033; Nazarenko et al., U.S. Patent No. 5,866,336, and Livalic et al., U.S. Patent 5,876,930.

Antibodies

[0140] The term “antibody” as used herein refers to an immunoglobulin molecule or immunologically active portion thereof, i.e., an antigen-binding portion. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab’)₂ fragments which can be generated by treating the antibody with an enzyme such as pepsin. An antibody sometimes is a polyclonal, monoclonal, recombinant (e.g., a chimeric or humanized), fully human, non-human (e.g., murine), or a single chain antibody. An antibody may have effector function and can fix complement, and is sometimes coupled to a toxin or imaging agent.

[0141] A full-length polypeptide or antigenic peptide fragment encoded by a nucleotide sequence referenced herein can be used as an immunogen or can be used to identify antibodies made with other immunogens, e.g., cells, membrane preparations, and the like. An antigenic peptide often includes at least 8 amino acid residues of the amino acid sequences encoded by a nucleotide sequence referenced herein, or substantially identical sequence thereof, and encompasses an epitope. Antigenic peptides

sometimes include 10 or more amino acids, 15 or more amino acids, 20 or more amino acids, or 30 or more amino acids. Hydrophilic and hydrophobic fragments of polypeptides sometimes are used as immunogens.

[0142] Epitopes encompassed by the antigenic peptide are regions located on the surface of the polypeptide (*e.g.*, hydrophilic regions) as well as regions with high antigenicity. For example, an Emi ni surface probability analysis of the human polypeptide sequence can be used to indicate the regions that have a particularly high probability of being localized to the surface of the polypeptide and are thus likely to constitute surface residues useful for targeting antibody production. The antibody may bind an epitope on any domain or region on polypeptides described herein.

[0143] Also, chimeric, humanized, and completely human antibodies are useful for applications which include repeated administration to subjects. Chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, can be made using standard recombinant DNA techniques. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson et al International Application No. PCT/US86/02269; Akira, et al European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison et al European Patent Application 173,494; Neuberger et al PCT International Publication No. WO 86/01533; Cabilly et al U.S. Patent No. 4,816,567; Cabilly et al European Patent Application 125,023; Better et al., Science 240: 1041-1043 (1988); Liu et al., Proc. Natl. Acad. Sci. USA 84: 3439-3443 (1987); Liu et al., J. Immunol. 139: 3521-3526 (1987); Sun et al., Proc. Natl. Acad. Sci. USA 84: 214-218 (1987); Nishimura et al., Canc. Res. 47: 999-1005 (1987); Wood et al., Nature 314: 446-449 (1985); and Shaw et al., J. Natl. Cancer Inst. 80: 1553-1559 (1988); Morrison, S. L., Science 229: 1202-1207 (1985); Oi et al., BioTechniques 4: 214 (1986); Winter U.S. Patent 5,225,539; Jones et al., Nature 321: 552-525 (1986); Verhoeyan et al., Science 239: 1534; and Beidler et al., J. Immunol. 141: 4053-4060 (1988).

[0144] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced using transgenic mice that are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. See, for example, Lonberg and Huszar, Int. Rev. Immunol. 13: 65-93 (1995); and U.S. Patent Nos. 5,625,126; 5,633,425; 5,569,825; 5,661,016; and 5,545,806. In addition, companies such as Abgenix, Inc. (Fremont, CA) and Medarex, Inc. (Princeton, NJ), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above. Completely human antibodies that recognize a selected epitope also can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody (*e.g.*, a murine antibody) is used to guide the selection of a completely human antibody recognizing the same epitope. This technology is described for example by Jespers et al., Bio/Technology 12: 899-903 (1994).

[0145] An antibody can be a single chain antibody. A single chain antibody (scFV) can be engineered (see, *e.g.*, Colcher et al., Ann. N Y Acad. Sci. 880: 263-80 (1999); and Reiter, Clin. Cancer

Res. 2: 245-52 (1996)). Single chain antibodies can be dimerized or multimerized to generate multivalent antibodies having specificities for different epitopes of the same target polypeptide.

[0146] Antibodies also may be selected or modified so that they exhibit reduced or no ability to bind an Fc receptor. For example, an antibody may be an isotype or subtype, fragment or other mutant, which does not support binding to an Fc receptor (*e.g.*, it has a mutagenized or deleted Fc receptor binding region).

[0147] Also, an antibody (or fragment thereof) may be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1 dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thiotepa chlorambucil, melphalan, carmustine (BCNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

[0148] Antibody conjugates can be used for modifying a given biological response. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a polypeptide such as tumor necrosis factor, gamma-interferon, alpha-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors. Also, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, for example.

[0149] An antibody (*e.g.*, monoclonal antibody) can be used to isolate target polypeptides by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, an antibody can be used to detect a target polypeptide (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the polypeptide. Antibodies can be used diagnostically to monitor polypeptide levels in tissue as part of a clinical testing procedure, *e.g.*, to determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance (*i.e.*, antibody labeling). Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of

suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H . Also, an antibody can be utilized as a test molecule for determining whether it can treat osteoarthritis, and as a therapeutic for administration to a subject for treating osteoarthritis.

[0150] An antibody can be made by immunizing with a purified antigen, or a fragment thereof, e.g., a fragment described herein, a membrane associated antigen, tissues, e.g., crude tissue preparations, whole cells, preferably living cells, lysed cells, or cell fractions.

[0151] Included herein are antibodies which bind only a native polypeptide, only denatured or otherwise non-native polypeptide, or which bind both, as well as those having linear or conformational epitopes. Conformational epitopes sometimes can be identified by selecting antibodies that bind to native but not denatured polypeptide. Also featured are antibodies that specifically bind to a polypeptide variant associated with osteoarthritis.

Methods for Identifying Candidate Therapeutics for Treating Osteoarthritis

[0152] Current therapies for the treatment of osteoarthritis have limited efficacy, limited tolerability and significant mechanism-based side effects, and few of the available therapies adequately address underlying defects. Current therapeutic approaches were largely developed in the absence of defined molecular targets or even a solid understanding of disease pathogenesis. Therefore, provided are methods of identifying candidate therapeutics that target biochemical pathways related to the development of osteoarthritis.

[0153] Thus, featured herein are methods for identifying a candidate therapeutic for treating osteoarthritis. The methods comprise contacting a test molecule with a target molecule in a system. A "target molecule" as used herein refers to a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleotide sequence referenced in Table B, a substantially identical nucleic acid thereof, or a fragment thereof, and an encoded polypeptide of the foregoing. The methods also comprise determining the presence or absence of an interaction between the test molecule and the target molecule, where the presence of an interaction between the test molecule and the nucleic acid or polypeptide identifies the test molecule as a candidate osteoarthritis therapeutic. The interaction between the test molecule and the target molecule may be quantified.

[0154] Test molecules and candidate therapeutics include, but are not limited to, compounds, antisense nucleic acids, siRNA molecules, ribozymes, polypeptides or proteins encoded by a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleotide sequence or other nucleotide sequence referenced in Table B, or a substantially identical sequence or fragment thereof, and immunotherapeutics (e.g., antibodies and HLA-presented polypeptide fragments).

A test molecule or candidate therapeutic may act as a modulator of target molecule concentration or target molecule function in a system. A “modulator” may agonize (*i.e.*, up-regulates) or antagonize (*i.e.*, down-regulates) a target molecule concentration partially or completely in a system by affecting such cellular functions as DNA replication and/or DNA processing (*e.g.*, DNA methylation or DNA repair), RNA transcription and/or RNA processing (*e.g.*, removal of intronic sequences and/or translocation of spliced mRNA from the nucleus), polypeptide production (*e.g.*, translation of the polypeptide from mRNA), and/or polypeptide post-translational modification (*e.g.*, glycosylation, phosphorylation, and proteolysis of pro-polypeptides). A modulator may also agonize or antagonize a biological function of a target molecule partially or completely, where the function may include adopting a certain structural conformation, interacting with one or more binding partners, ligand binding, catalysis (*e.g.*, phosphorylation, dephosphorylation, hydrolysis, methylation, and isomerization), and an effect upon a cellular event (*e.g.*, effecting progression of osteoarthritis). Any modulator may be utilized, such as a peptidyl arginine deiminase modulator (*e.g.*, *PADI2* likely is a peptidyl arginine deiminase) described in WO-09851784 and WO0244360A2 or an apolipoprotein (*e.g.*, *APOB* includes an apolipoprotein domain) modulatory compound (*e.g.*, WO-2004017969, WO-03002533, US 6,369,075, WO-02098839, WO-02098871, WO-00177077, WO-00153260, WO-00105767), antibody (*e.g.*, WO-9600903A1, US 6,309,844 and US 5,330,910) or antisense molecule (*e.g.*, WO03011887A2 and WO03097662A1).

[0155] As used herein, the term “system” refers to a cell free *in vitro* environment and a cell-based environment such as a collection of cells, a tissue, an organ, or an organism. A system is “contacted” with a test molecule in a variety of manners, including adding molecules in solution and allowing them to interact with one another by diffusion, cell injection, and any administration routes in an animal. As used herein, the term “interaction” refers to an effect of a test molecule on test molecule, where the effect sometimes is binding between the test molecule and the target molecule, and sometimes is an observable change in cells, tissue, or organism.

[0156] There are many standard methods for detecting the presence or absence of interaction between a test molecule and a target molecule. For example, titrametric, acidimetric, radiometric, NMR, monolayer, polarographic, spectrophotometric, fluorescent, and ESR assays probative of a target molecule interaction may be utilized. Examples of G protein-coupled receptor assays are known, for example, and are described in WO-0242461 and WO-04013285.

[0157] *ADAMTS2* activity and/or *ADAMTS2* interactions can be detected and quantified using assays known in the art. For example, an immunoprecipitation assay or a kinase activity assay that employs a kinase-inactivated MEK can be utilized. Kinase inactivated MEKs are known in the art, such as a MEK that includes the mutation K97M. In these assays, mammalian cells (*e.g.*, COS or NIH-3T3) are transiently transfected with constructs expressing *ADAMTS2*, and in addition, the cells are co-transfected with oncogenic RAS or SRC or both. Oncogenic RAS or SRC activates *ADAMTS2* kinase activity. *ADAMTS2* is immunoprecipitated from cell extracts using a monoclonal antibody (*e.g.*, 9E 10) or a polyclonal antibody (*e.g.*, from rabbit) specific for a unique peptide from *ADAMTS2*. *ADAMTS2* is

then resuspended in assay buffer containing GST-Mek1 or GST-Mek2 and/or GST-ERK2. In addition, [gamma 32 P] ATP can be added to detect and/or quantify phosphorylation activity. Samples are incubated for 5-30 minutes at 30°C, and then the reaction is terminated by addition of EDTA. The samples are centrifuged and the supernatant fractions are collected. Phosphorylation activity is detected using one of two methods: (i) activity of GST-ERK2 kinase can be measured using MBP (myelin basic protein, a substrate for ERK) as substrate, or (ii) following incubation of immunoprecipitated *ADAMTS2* in reaction buffer containing GST-ERK and [gamma 32 P] ATP, transfer of labeled ATP to kinase-dead ERK can be quantified by a phosphor-imager or densitometer following PAGE separation of polypeptide products (phosphorylated and non-phosphorylated forms). These types of assays are described in Weber et al., *Oncogene* 19: 169-176 (2000); Mason et al., *EMBO J.* 18: 2137-2148 (1999); Marais et al., *J. Biol. Chem.* 272: 4378-4383 (1997); Marais et al., *EMBO J.* 14: 3136-3145 (1995).

[0158] As noted above, *ADAMTS2* includes a domain having metalloprotease activity, and modulators of such activity are known. Examples of such modulators are set forth in WO03063762A2; WO-09937625; WO-09918076; WO-09838163; WO-09837877; WO9947550A1; WO0177092A1; WO0040577A1; WO9942436A1; WO9838163A1; WO9837877A1; WO04014379A1; WO03106381A2; WO03014098A1; WO03014092A1 and WO02096426A1.

[0159] Test molecule/target molecule interactions can be detected and/or quantified using assays known in the art. For example, an interaction can be determined by labeling the test molecule and/or the target molecule, where the label is covalently or non-covalently attached to the test molecule or target molecule. The label is sometimes a radioactive molecule such as 125 I, 131 I, 35 S or 3 H, which can be detected by direct counting of radioemission or by scintillation counting. Also, enzymatic labels such as horseradish peroxidase, alkaline phosphatase, or luciferase may be utilized where the enzymatic label can be detected by determining conversion of an appropriate substrate to product. In addition, presence or absence of an interaction can be determined without labeling. For example, a microphysiometer (e.g., Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indication of an interaction between a test molecule and target molecule (McConnell, H. M. et al., *Science* 257: 1906-1912 (1992)).

[0160] In cell-based systems, cells typically include a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleotide sequence referenced in Table B, an encoded polypeptide, or substantially identical nucleic acid or polypeptide thereof, and are often of mammalian origin, although the cell can be of any origin. Whole cells, cell homogenates, and cell fractions (e.g., cell membrane fractions) can be subjected to analysis. Where interactions between a test molecule with a target polypeptide are monitored, soluble and/or membrane bound forms of the polypeptide may be utilized. Where membrane-bound forms of the polypeptide are used, it may be desirable to utilize a solubilizing agent. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®,

Isotridecypoly(ethylene glycol ether)_n, 3-[(3-cholamidopropyl)dimethylamminio]-1-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamminio]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl-N,N-dimethyl-3-ammonio-1-propane sulfonate.

[0161] An interaction between a test molecule and target molecule also can be detected by monitoring fluorescence energy transfer (FET) (*see, e.g.*, Lakowicz *et al.*, U.S. Patent No. 5,631,169; Stavrianopoulos *et al.* U.S. Patent No. 4,868,103). A fluorophore label on a first, “donor” molecule is selected such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, “acceptor” molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the “donor” polypeptide molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the “acceptor” molecule label may be differentiated from that of the “donor”. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, the spatial relationship between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the “acceptor” molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter).

[0162] In another embodiment, determining the presence or absence of an interaction between a test molecule and a target molecule can be effected by monitoring surface plasmon resonance (*see, e.g.*, Sjolander & Urbanicz, *Anal. Chem.* 63: 2338-2345 (1991) and Szabo *et al.*, *Curr. Opin. Struct. Biol.* 5: 699-705 (1995)). “Surface plasmon resonance” or “biomolecular interaction analysis (BIA)” can be utilized to detect biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

[0163] In another embodiment, the target molecule or test molecules are anchored to a solid phase, facilitating the detection of target molecule/test molecule complexes and separation of the complexes from free, uncomplexed molecules. The target molecule or test molecule is immobilized to the solid support. In an embodiment, the target molecule is anchored to a solid surface, and the test molecule, which is not anchored, can be labeled, either directly or indirectly, with detectable labels discussed herein.

[0164] It may be desirable to immobilize a target molecule, an anti-target molecule antibody, and/or test molecules to facilitate separation of target molecule/test molecule complexes from uncomplexed forms, as well as to accommodate automation of the assay. The attachment between a test molecule and/or target molecule and the solid support may be covalent or non-covalent (*see, e.g.*, U.S. Patent No. 6,022,688 for non-covalent attachments). The solid support may be one or more surfaces of the system, such as one or more surfaces in each well of a microtiter plate, a surface of a silicon wafer, a surface of a bead (*see, e.g.*, Lam, *Nature* 354: 82-84 (1991)) that is optionally linked to another solid

support, or a channel in a microfluidic device, for example. Types of solid supports, linker molecules for covalent and non-covalent attachments to solid supports, and methods for immobilizing nucleic acids and other molecules to solid supports are well known (*see, e.g.*, U.S. Patent Nos. 6,261,776; 5,900,481; 6,133,436; and 6,022,688; and WIPO publication WO 01/18234).

[0165] In an embodiment, target molecule may be immobilized to surfaces via biotin and streptavidin. For example, biotinylated target polypeptide can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In another embodiment, a target polypeptide can be prepared as a fusion polypeptide. For example, glutathione-S-transferase/target polypeptide fusion can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivitized microtiter plates, which are then combined with a test molecule under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtiter plate wells are washed to remove any unbound components, or the matrix is immobilized in the case of beads, and complex formation is determined directly or indirectly as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of target molecule binding or activity is determined using standard techniques.

[0166] In an embodiment, the non-immobilized component is added to the coated surface containing the anchored component. After the reaction is complete, unreacted components are removed (*e.g.*, by washing) under conditions such that a significant percentage of complexes formed will remain immobilized to the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of manners. Where the previously non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the previously non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface, *e.g.*, by adding a labeled antibody specific for the immobilized component, where the antibody, in turn, can be directly labeled or indirectly labeled with, *e.g.*, a labeled anti-Ig antibody.

[0167] In another embodiment, an assay is performed utilizing antibodies that specifically bind target molecule or test molecule but do not interfere with binding of the target molecule to the test molecule. Such antibodies can be derivitized to a solid support, and unbound target molecule may be immobilized by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the target molecule.

[0168] Cell free assays also can be conducted in a liquid phase. In such an assay, reaction products are separated from unreacted components, by any of a number of standard techniques, including but not limited to: differential centrifugation (*see, e.g.*, Rivas, G., and Minton, *Trends Biochem Sci Aug;18(8): 284-7 (1993)*); chromatography (gel filtration chromatography, ion-exchange chromatography);

electrophoresis (*see, e.g., Ausubel et al., eds. Current Protocols in Molecular Biology, J. Wiley: New York (1999)*); and immunoprecipitation (*see, e.g., Ausubel et al., eds., supra*). Media and chromatographic techniques are known to one skilled in the art (*see, e.g., Heegaard, J Mol. Recognit. Winter; 11(1-6): 141-8 (1998); Hage & Tweed, J. Chromatogr. B Biomed. Sci. Appl. Oct 10; 699 (1-2): 499-525 (1997)*). Further, fluorescence energy transfer may also be conveniently utilized, as described herein, to detect binding without further purification of the complex from solution.

[0169] In another embodiment, modulators of target molecule expression are identified. For example, a cell or cell free mixture is contacted with a candidate compound and the expression of target mRNA or target polypeptide is evaluated relative to the level of expression of target mRNA or target polypeptide in the absence of the candidate compound. When expression of target mRNA or target polypeptide is greater in the presence of the candidate compound than in its absence, the candidate compound is identified as an agonist of target mRNA or target polypeptide expression. Alternatively, when expression of target mRNA or target polypeptide is less (*e.g., less with statistical significance*) in the presence of the candidate compound than in its absence, the candidate compound is identified as an antagonist or inhibitor of target mRNA or target polypeptide expression. The level of target mRNA or target polypeptide expression can be determined by methods described herein.

[0170] In another embodiment, binding partners that interact with a target molecule are detected. The target molecules can interact with one or more cellular or extracellular macromolecules, such as polypeptides *in vivo*, and these interacting molecules are referred to herein as “binding partners.” Binding partners can agonize or antagonize target molecule biological activity. Also, test molecules that agonize or antagonize interactions between target molecules and binding partners can be useful as therapeutic molecules as they can up-regulate or down-regulate target molecule activity *in vivo* and thereby treat osteoarthritis.

[0171] Binding partners of target molecules can be identified by methods known in the art. For example, binding partners may be identified by lysing cells and analyzing cell lysates by electrophoretic techniques. Alternatively, a two-hybrid assay or three-hybrid assay can be utilized (*see, e.g., U.S. Patent No. 5,283,317; Zervos et al., Cell 72:223-232 (1993); Madura et al., J. Biol. Chem. 268: 12046-12054 (1993); Bartel et al., Biotechniques 14: 920-924 (1993); Iwabuchi et al., Oncogene 8: 1693-1696 (1993); and Brent WO94/10300*). A two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. The assay often utilizes two different DNA constructs. In one construct, a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleic acid referenced in Table B (sometimes referred to as the “bait”) is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g., GAL-4*). In another construct, a DNA sequence from a library of DNA sequences that encodes a potential binding partner (sometimes referred to as the “prey”) is fused to a gene that encodes an activation domain of the known transcription factor. Sometimes, a *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* or *APOL3* nucleic acid or other nucleic acid referenced in Table B can be fused to the activation domain. If the “bait” and

the “prey” molecules interact *in vivo*, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to identify the potential binding partner.

[0172] In an embodiment for identifying test molecules that antagonize or agonize complex formation between target molecules and binding partners, a reaction mixture containing the target molecule and the binding partner is prepared, under conditions and for a time sufficient to allow complex formation. The reaction mixture often is provided in the presence or absence of the test molecule. The test molecule can be included initially in the reaction mixture, or can be added at a time subsequent to the addition of the target molecule and its binding partner. Control reaction mixtures are incubated without the test molecule or with a placebo. Formation of any complexes between the target molecule and the binding partner then is detected. Decreased formation of a complex in the reaction mixture containing test molecule as compared to in a control reaction mixture indicates that the molecule antagonizes target molecule/binding partner complex formation. Alternatively, increased formation of a complex in the reaction mixture containing test molecule as compared to in a control reaction mixture indicates that the molecule agonizes target molecule/binding partner complex formation. In another embodiment, complex formation of target molecule/binding partner can be compared to complex formation of mutant target molecule/binding partner (*e.g.*, amino acid modifications in a target polypeptide). Such a comparison can be important in those cases where it is desirable to identify test molecules that modulate interactions of mutant but not non-mutated target gene products.

[0173] The assays can be conducted in a heterogeneous or homogeneous format. In heterogeneous assays, target molecule and/or the binding partner are immobilized to a solid phase, and complexes are detected on the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the molecules being tested. For example, test compounds that agonize target molecule/binding partner interactions can be identified by conducting the reaction in the presence of the test molecule in a competition format. Alternatively, test molecules that agonize preformed complexes, *e.g.*, molecules with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed.

[0174] In a heterogeneous assay embodiment, the target molecule or the binding partner is anchored onto a solid surface (*e.g.*, a microtiter plate), while the non-anchored species is labeled, either directly or indirectly. The anchored molecule can be immobilized by non-covalent or covalent attachments. Alternatively, an immobilized antibody specific for the molecule to be anchored can be used to anchor the molecule to the solid surface. The partner of the immobilized species is exposed to the coated surface with or without the test molecule. After the reaction is complete, unreacted

components are removed (*e.g.*, by washing) such that a significant portion of any complexes formed will remain immobilized on the solid surface. Where the non-immobilized species is pre-labeled, the detection of label immobilized on the surface is indicative of complex. Where the non-immobilized species is not pre-labeled, an indirect label can be used to detect complexes anchored to the surface; *e.g.*, by using a labeled antibody specific for the initially non-immobilized species. Depending upon the order of addition of reaction components, test compounds that inhibit complex formation or that disrupt preformed complexes can be detected.

[0175] In another embodiment, the reaction can be conducted in a liquid phase in the presence or absence of test molecule, where the reaction products are separated from unreacted components, and the complexes are detected (*e.g.*, using an immobilized antibody specific for one of the binding components to anchor any complexes formed in solution, and a labeled antibody specific for the other partner to detect anchored complexes). Again, depending upon the order of addition of reactants to the liquid phase, test compounds that inhibit complex or that disrupt preformed complexes can be identified.

[0176] In an alternate embodiment, a homogeneous assay can be utilized. For example, a preformed complex of the target gene product and the interactive cellular or extracellular binding partner product is prepared. One or both of the target molecule or binding partner is labeled, and the signal generated by the label(s) is quenched upon complex formation (*e.g.*, U.S. Patent No. 4,109,496 that utilizes this approach for immunoassays). Addition of a test molecule that competes with and displaces one of the species from the preformed complex will result in the generation of a signal above background. In this way, test substances that disrupt target molecule/binding partner complexes can be identified.

[0177] Candidate therapeutics for treating osteoarthritis are identified from a group of test molecules that interact with a target molecule. Test molecules are normally ranked according to the degree with which they modulate (*e.g.*, agonize or antagonize) a function associated with the target molecule (*e.g.*, DNA replication and/or processing, RNA transcription and/or processing, polypeptide production and/or processing, and/or biological function/activity), and then top ranking modulators are selected. Also, pharmacogenomic information described herein can determine the rank of a modulator. The top 10% of ranked test molecules often are selected for further testing as candidate therapeutics, and sometimes the top 15%, 20%, or 25% of ranked test molecules are selected for further testing as candidate therapeutics. Candidate therapeutics typically are formulated for administration to a subject.

Therapeutic Formulations

[0178] Formulations and pharmaceutical compositions typically include in combination with a pharmaceutically acceptable carrier one or more target molecule modulators. The modulator often is a test molecule identified as having an interaction with a target molecule by a screening method described above. The modulator may be a compound, an antisense nucleic acid, a ribozyme, an antibody, or a binding partner. Also, formulations may comprise a target polypeptide or fragment thereof in combination with a pharmaceutically acceptable carrier, where the polypeptide or fragment sometimes

has an *APOL3* biological activity (*e.g.*, apolipoprotein activity), and sometimes includes all or part of an apolipoprotein domain.

[0179] Formulations or pharmaceutical compositions typically include in combination with a pharmaceutically acceptable carrier, a compound, an antisense nucleic acid, a ribozyme, an antibody, a binding partner that interacts with an *ADAMTS2* polypeptide, a *ADAMTS2* nucleic acid, or a fragment thereof. The formulated molecule may be one that is identified by a screening method described above. Also, formulations may comprise a *ADAMTS2* polypeptide or fragment thereof, where the *ADAMTS2* polypeptide contains an isoleucine at position 245 of SEQ ID NO: 44, and a pharmaceutically acceptable carrier. Also, formulations may comprise an active *ADAMTS2* polypeptide or fragment thereof, where *ADAMTS2* polypeptide fragments having activity are selected from amino acids 252-1211, 253-1211, 254-1211, 255-1211, 256-1211, 257-1211, 258-1211, 259-1211 or 260-1211 of SEQ ID NO: 44, where it is understood that the active form of *ADAMTS2* does not contain the propeptide domain. As used herein, the term "pharmaceutically acceptable carrier" includes solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Supplementary active compounds can also be incorporated into the compositions.

[0180] As used herein, the term "pharmaceutically acceptable carrier" includes solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Supplementary active compounds can also be incorporated into the compositions. Pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0181] A pharmaceutical composition typically is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0182] Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules, *e.g.*, gelatin capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as

microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0183] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0184] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0185] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0186] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally

known in the art. Molecules can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0187] In one embodiment, active molecules are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[0188] It is advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0189] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Molecules which exhibit high therapeutic indices are preferred. While molecules that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

[0190] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such molecules lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any molecules used in the methods described herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0191] As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, sometimes about 0.01 to 25 mg/kg body weight, often about 0.1 to 20 mg/kg body weight, and more often about 1 to 10 mg/kg, 2 to 9

mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The protein or polypeptide can be administered one time per week for between about 1 to 10 weeks, sometimes between 2 to 8 weeks, often between about 3 to 7 weeks, and more often for about 4, 5, or 6 weeks. The skilled artisan will appreciate that certain factors may influence the dosage and timing required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

[0192] With regard to polypeptide formulations, featured herein is a method for treating osteoarthritis in a subject, which comprises contacting one or more cells in the subject with a first polypeptide, where the subject comprises a second polypeptide having one or more polymorphic variations associated with cancer, and where the first polypeptide comprises fewer polymorphic variations associated with cancer than the second polypeptide. The first and second polypeptides are encoded by a nucleic acid which comprises a nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B; a nucleotide sequence which encodes a polypeptide consisting of an amino acid sequence encoded by a nucleotide sequence referenced in SEQ ID NO: 1-13 or referenced in Table B; a nucleotide sequence which encodes a polypeptide that is 90% or more identical to an amino acid sequence encoded by a nucleotide sequence of SEQ ID NO: 1-13 or referenced in Table B and a nucleotide sequence 90% or more identical to a nucleotide sequence in SEQ ID NO: 1-13 or referenced in Table B. The subject often is a human.

[0193] For antibodies, a dosage of 0.1 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg) is often utilized. If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is often appropriate. Generally, partially human antibodies and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (*e.g.*, into the brain). A method for lipidation of antibodies is described by Cruikshank *et al.*, *J. Acquired Immune Deficiency Syndromes and Human Retrovirology* 14:193 (1997).

[0194] Antibody conjugates can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a polypeptide such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors. Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

[0195] For compounds, exemplary doses include milligram or microgram amounts of the compound per kilogram of subject or sample weight, for example, about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram. It is understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in order to modulate expression or activity of a polypeptide or nucleic acid described herein, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

[0196] With regard to nucleic acid formulations, gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (*see, e.g.*, U.S. Patent 5,328,470) or by stereotactic injection (*see e.g.*, Chen *et al.*, (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). Pharmaceutical preparations of gene therapy vectors can include a gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells (*e.g.*, retroviral vectors) the pharmaceutical preparation can include one or more cells which produce the gene delivery system. Examples of gene delivery vectors are described herein.

Therapeutic Methods

[0197] A therapeutic formulation described above can be administered to a subject in need of a therapeutic for inducing a desired biological response. Therapeutic formulations can be administered by any of the paths described herein. With regard to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from pharmacogenomic analyses described herein.

[0198] As used herein, the term "treatment" is defined as the application or administration of a therapeutic formulation to a subject, or application or administration of a therapeutic agent to an isolated tissue or cell line from a subject with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect osteoarthritis, symptoms of osteoarthritis or a predisposition towards osteoarthritis. A therapeutic formulation includes, but is not limited to, small molecules, peptides, antibodies, ribozymes and antisense oligonucleotides. Administration of a therapeutic formulation can occur prior to the manifestation of symptoms characteristic of osteoarthritis, such that osteoarthritis is prevented or delayed in its progression. The appropriate therapeutic composition can be determined based on screening assays described herein.

[0199] As discussed, successful treatment of osteoarthritis can be brought about by techniques that serve to agonize target molecule expression or function, or alternatively, antagonize target molecule expression or function. These techniques include administration of modulators that include, but are not limited to, small organic or inorganic molecules; antibodies (including, for example, polyclonal, monoclonal, humanized, anti-idiotypic, chimeric or single chain antibodies, and Fab, F(ab')₂ and Fab expression library fragments, scFV molecules, and epitope-binding fragments thereof); and peptides, phosphopeptides, or polypeptides.

[0200] Further, antisense and ribozyme molecules that inhibit expression of the target gene can also be used to reduce the level of target gene expression, thus effectively reducing the level of target gene activity. Still further, triple helix molecules can be utilized in reducing the level of target gene activity. Antisense, ribozyme and triple helix molecules are discussed above. It is possible that the use of antisense, ribozyme, and/or triple helix molecules to reduce or inhibit mutant gene expression can also reduce or inhibit the transcription (triple helix) and/or translation (antisense, ribozyme) of mRNA produced by normal target gene alleles, such that the concentration of normal target gene product present can be lower than is necessary for a normal phenotype. In such cases, nucleic acid molecules that encode and express target gene polypeptides exhibiting normal target gene activity can be introduced into cells via gene therapy method. Alternatively, in instances in that the target gene encodes an extracellular polypeptide, it can be preferable to co-administer normal target gene polypeptide into the cell or tissue in order to maintain the requisite level of cellular or tissue target gene activity.

[0201] Another method by which nucleic acid molecules may be utilized in treating or preventing osteoarthritis is use of aptamer molecules specific for target molecules. Aptamers are nucleic acid molecules having a tertiary structure which permits them to specifically bind to ligands (*see, e.g., Osborne, et al., Curr. Opin. Chem. Biol.* 1(1): 5-9 (1997); and Patel, D. J., *Curr. Opin. Chem. Biol.* Jun; 1(1): 32-46 (1997)).

[0202] Yet another method of utilizing nucleic acid molecules for osteoarthritis treatment is gene therapy, which can also be referred to as allele therapy. Provided herein is a gene therapy method for treating osteoarthritis in a subject, which comprises contacting one or more cells in the subject or from the subject with a nucleic acid having a first nucleotide sequence (*e.g., the first nucleotide sequence is identical to or substantially identical to a nucleotide sequence of SEQ ID NO: 1-13 or other nucleotide sequence referenced in Table B*). Genomic DNA in the subject comprises a second nucleotide sequence having one or more polymorphic variations associated with osteoarthritis (*e.g., the second nucleotide sequence is identical to or substantially identical to a nucleotide sequence of SEQ ID NO: 1-13 or other nucleotide sequence referenced in Table B*). The first and second nucleotide sequences typically are substantially identical to one another, and the first nucleotide sequence comprises fewer polymorphic variations associated with osteoarthritis than the second nucleotide sequence. The first nucleotide sequence may comprise a gene sequence that encodes a full-length polypeptide or a fragment thereof. The subject is often a human. Allele therapy methods often are utilized in conjunction with a method of

first determining whether a subject has genomic DNA that includes polymorphic variants associated with osteoarthritis.

[0203] In a certain embodiment, the method often comprises supplementing arthritis-associated *ADAMTS2* polypeptide with a non-arthritis-associated *ADAMTS2* polypeptide or fragment thereof, where the non-arthritis-associated form of *ADAMTS2* contains an isoleucine at position 245 of SEQ ID NO: 44 having enzymatic activity. The arthritis-associated *ADAMTS2* polypeptide sometimes contains a valine at position 245 of SEQ ID NO: 44 having an altered enzymatic activity varying from the non-arthritis-associated polypeptide.

[0204] In an embodiment, provided is a method of increasing the synthesis of procollagen II comprising providing or administering to individuals in need of increasing levels of type II collagen the pharmaceutical or physiologically acceptable composition comprising active human *ADAMTS2* protein or fragment thereof, where *ADAMTS2* polypeptide fragments having activity are selected from amino acids 252-1211, 253-1211, 254-1211, 255-1211, 256-1211, 257-1211, 258-1211, 259-1211 or 260-1211 of SEQ ID NO: 44, where it is understood that the active form of *ADAMTS2* does not contain the propeptide domain.

[0205] In another embodiment, provided herein is a method of increasing the synthesis of procollagen II comprising providing or administering to individuals in need of increasing levels of type II collagen the pharmaceutical or physiologically acceptable composition comprising an enzyme or molecule capable of cleaving *ADAMTS2* propeptide, *e.g.*, a furin-type endopeptidase or N-ethylmaleimide described herein

[0206] In another allele therapy embodiment, provided herein is a method which comprises contacting one or more cells in the subject or from the subject with a polypeptide encoded by a nucleic acid having a first nucleotide sequence (*e.g.*, the first nucleotide sequence is identical to or substantially identical to the nucleotide sequence of SEQ ID NO: 1-13 or other nucleotide sequence referenced in Table B). Genomic DNA in the subject comprises a second nucleotide sequence having one or more polymorphic variations associated with osteoarthritis (*e.g.*, the second nucleotide sequence is identical to or substantially identical to a nucleotide sequence of SEQ ID NO: 1-13 or other nucleotide sequence referenced in Table B). The first and second nucleotide sequences typically are substantially identical to one another, and the first nucleotide sequence comprises fewer polymorphic variations associated with osteoarthritis than the second nucleotide sequence. The first nucleotide sequence may comprise a gene sequence that encodes a full-length polypeptide or a fragment thereof. The subject is often a human.

[0207] For antibody-based therapies, antibodies can be generated that are both specific for target molecules and that reduce target molecule activity. Such antibodies may be administered in instances where antagonizing a target molecule function is appropriate for the treatment of osteoarthritis.

[0208] In circumstances where stimulating antibody production in an animal or a human subject by injection with a target molecule is harmful to the subject, it is possible to generate an immune response against the target molecule by use of anti-idiotypic antibodies (*see, e.g.*, Herlyn, *Ann. Med.*; 31(1): 66-78

(1999); and Bhattacharya-Chatterjee & Foon, *Cancer Treat. Res.*; 94: 51-68 (1998)). Introducing an anti-idiotypic antibody to a mammal or human subject often stimulates production of anti-anti-idiotypic antibodies, which typically are specific to the target molecule. Vaccines directed to osteoarthritis also may be generated in this fashion.

[0209] In instances where the target molecule is intracellular and whole antibodies are used, internalizing antibodies may be preferred. Lipofectin or liposomes can be used to deliver the antibody or a fragment of the Fab region that binds to the target antigen into cells. Where fragments of the antibody are used, the smallest inhibitory fragment that binds to the target antigen is preferred. For example, peptides having an amino acid sequence corresponding to the Fv region of the antibody can be used. Alternatively, single chain neutralizing antibodies that bind to intracellular target antigens can also be administered. Such single chain antibodies can be administered, for example, by expressing nucleotide sequences encoding single-chain antibodies within the target cell population (*see, e.g., Marasco et al., Proc. Natl. Acad. Sci. USA 90: 7889-7893 (1993)*).

[0210] Modulators can be administered to a patient at therapeutically effective doses to treat osteoarthritis. A therapeutically effective dose refers to an amount of the modulator sufficient to result in amelioration of symptoms of osteoarthritis. Toxicity and therapeutic efficacy of modulators can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.,* for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Modulators that exhibit large therapeutic indices are preferred. While modulators that exhibit toxic side effects can be used, care should be taken to design a delivery system that targets such molecules to the site of affected tissue in order to minimize potential damage to uninfected cells, thereby reducing side effects.

[0211] Data obtained from cell culture assays and animal studies can be used in formulating a range of dosages for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the methods described herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (*i.e.,* the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

[0212] Another example of effective dose determination for an individual is the ability to directly assay levels of “free” and “bound” compound in the serum of the test subject. Such assays may utilize antibody mimics and/or “biosensors” that have been created through molecular imprinting techniques. Molecules that modulate target molecule activity are used as a template, or “imprinting molecule”, to spatially organize polymerizable monomers prior to their polymerization with catalytic reagents. The

subsequent removal of the imprinted molecule leaves a polymer matrix which contains a repeated “negative image” of the compound and is able to selectively rebind the molecule under biological assay conditions. A detailed review of this technique can be seen in Ansell *et al.*, *Current Opinion in Biotechnology* 7: 89-94 (1996) and in Shea, *Trends in Polymer Science* 2: 166-173 (1994). Such “imprinted” affinity matrixes are amenable to ligand-binding assays, whereby the immobilized monoclonal antibody component is replaced by an appropriately imprinted matrix. An example of the use of such matrixes in this way can be seen in Vlatakis, *et al.*, *Nature* 361: 645-647 (1993). Through the use of isotope-labeling, the “free” concentration of compound which modulates target molecule expression or activity readily can be monitored and used in calculations of IC_{50} . Such “imprinted” affinity matrixes can also be designed to include fluorescent groups whose photon-emitting properties measurably change upon local and selective binding of target compound. These changes readily can be assayed in real time using appropriate fiberoptic devices, in turn allowing the dose in a test subject to be quickly optimized based on its individual IC_{50} . An example of such a “biosensor” is discussed in Kriz *et al.*, *Analytical Chemistry* 67: 2142-2144 (1995).

[0213] The examples set forth below are intended to illustrate but not limit the invention.

Examples

[0214] In the following studies a group of subjects was selected according to specific parameters relating to osteoarthritis. Nucleic acid samples obtained from individuals in the study group were subjected to genetic analysis, which identified associations between osteoarthritis and certain polymorphic variants in the following genes: *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *PELI2*, *LOXL1*, *CASPR4*, *GPR50* or *APOL3* (herein referred to as “Targets”). The polymorphisms were genotyped again in two replication cohorts consisting of individuals selected for OA. In addition, SNPs proximal to the incident polymorphism in *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CASPR4* and *APOL3* regions were identified and allelotyped in OA case and control pools. Methods are described for producing target polypeptides encoded by the nucleic acids of Table B *in vitro* or *in vivo*, which can be utilized in methods that screen test molecules for those that interact with target polypeptides. Test molecules identified as interactors with target polypeptides can be screened further as osteoarthritis therapeutics.

Example 1

Samples and Pooling Strategies

Sample Selection

[0215] Blood samples were collected from individuals diagnosed with knee osteoarthritis, which were referred to as case samples. Also, blood samples were collected from individuals not diagnosed with knee osteoarthritis as gender and age-matched controls. A database was created that listed all

phenotypic trait information gathered from individuals for each case and control sample. Genomic DNA was extracted from each of the blood samples for genetic analyses.

DNA Extraction from Blood Samples

[0216] Six to ten milliliters of whole blood was transferred to a 50 ml tube containing 27 ml of red cell lysis solution (RCL). The tube was inverted until the contents were mixed. Each tube was incubated for 10 minutes at room temperature and inverted once during the incubation. The tubes were then centrifuged for 20 minutes at 3000 x g and the supernatant was carefully poured off. 100-200 µl of residual liquid was left in the tube and was pipetted repeatedly to resuspend the pellet in the residual supernatant. White cell lysis solution (WCL) was added to the tube and pipetted repeatedly until completely mixed. While no incubation was normally required, the solution was incubated at 37°C or room temperature if cell clumps were visible after mixing until the solution was homogeneous. 2 ml of protein precipitation was added to the cell lysate. The mixtures were vortexed vigorously at high speed for 20 sec to mix the protein precipitation solution uniformly with the cell lysate, and then centrifuged for 10 minutes at 3000 x g. The supernatant containing the DNA was then poured into a clean 15 ml tube, which contained 7 ml of 100% isopropanol. The samples were mixed by inverting the tubes gently until white threads of DNA were visible. Samples were centrifuged for 3 minutes at 2000 x g and the DNA was visible as a small white pellet. The supernatant was decanted and 5 ml of 70% ethanol was added to each tube. Each tube was inverted several times to wash the DNA pellet, and then centrifuged for 1 minute at 2000 x g. The ethanol was decanted and each tube was drained on clean absorbent paper. The DNA was dried in the tube by inversion for 10 minutes, and then 1000 µl of 1X TE was added. The size of each sample was estimated, and less TE buffer was added during the following DNA hydration step if the sample was smaller. The DNA was allowed to rehydrate overnight at room temperature, and DNA samples were stored at 2-8°C.

[0217] DNA was quantified by placing samples on a hematology mixer for at least 1 hour. DNA was serially diluted (typically 1:80, 1:160, 1:320, and 1:640 dilutions) so that it would be within the measurable range of standards. 125 µl of diluted DNA was transferred to a clear U-bottom microtitre plate, and 125 µl of 1X TE buffer was transferred into each well using a multichannel pipette. The DNA and 1X TE were mixed by repeated pipetting at least 15 times, and then the plates were sealed. 50 µl of diluted DNA was added to wells A5-H12 of a black flat bottom microtitre plate. Standards were inverted six times to mix them, and then 50 µl of 1X TE buffer was pipetted into well A1, 1000 ng/ml of standard was pipetted into well A2, 500 ng/ml of standard was pipetted into well A3, and 250 ng/ml of standard was pipetted into well A4. PicoGreen (Molecular Probes, Eugene, Oregon) was thawed and freshly diluted 1:200 according to the number of plates that were being measured. PicoGreen was vortexed and then 50µl was pipetted into all wells of the black plate with the diluted DNA. DNA and PicoGreen were mixed by pipetting repeatedly at least 10 times with the multichannel pipette. The plate was placed into a Fluoroskan Ascent Machine (microplate fluorometer produced by Labsystems) and

the samples were allowed to incubate for 3 minutes before the machine was run using filter pairs 485 nm excitation and 538 nm emission wavelengths. Samples having measured DNA concentrations of greater than 450 ng/μl were re-measured for conformation. Samples having measured DNA concentrations of 20 ng/μl or less were re-measured for confirmation.

Pooling Strategies – Discovery Cohort

[0218] Samples were derived from the Nottingham knee OA family study (UK) where index cases were identified through a knee replacement registry. Siblings were approached and assessed with knee x-rays and assigned status as affected or unaffected. In all 1,157 individuals were available. In order to create same-sex pools of appropriate sizes, 335 unrelated female individuals with OA from the Nottingham OA sample were selected for the case pool. The control pool was made up of unrelated female individuals from the St. Thomas twin study (England) with normal knee x-rays and without other indications of OA, regardless of anatomical location, as well as lacking family history of OA. The St. Thomas twin study consists of Caucasian, female participants from the St. Thomas' Hospital, London, adult-twin registry, which is a voluntary registry of >4,000 twin pairs ranging from 18 to 76 years of age. The female case samples and female control samples are described further in Table 1 below.

[0219] A select set of samples from each group were utilized to generate pools, and one pool was created for each group. Each individual sample in a pool was represented by an equal amount of genomic DNA. For example, where 25 ng of genomic DNA was utilized in each PCR reaction and there were 200 individuals in each pool, each individual would provide 125 pg of genomic DNA. Inclusion or exclusion of samples for a pool was based upon the following criteria: the sample was derived from an individual characterized as Caucasian; the sample was derived from an individual of British paternal and maternal descent; case samples were derived from individuals diagnosed with specific knee osteoarthritis (OA) and were recruited from an OA knee replacement clinic. Control samples were derived from individuals free of OA, family history of OA, and rheumatoid arthritis. Also, sufficient genomic DNA was extracted from each blood sample for all allelotyping and genotyping reactions performed during the study. Phenotype information from each individual was collected and included age of the individual, gender, family history of OA, general medical information (e.g., height, weight, thyroid disease, diabetes, psoriasis, hysterectomy), joint history (previous and current symptoms, joint-related operations, age at onset of symptoms, date of primary diagnosis, age of individual as of primary diagnosis and order of involvement), and knee-related findings (crepitus, restricted passive movement, bony swelling/deformity). Additional knee information included knee history, current symptoms, any major knee injury, meniscectomy, knee replacement surgery, age of surgery, and treatment history (including hormone replace therapy (HRT)). Samples that met these criteria were added to appropriate pools based on disease status.

[0220] The selection process yielded the pools set forth in Table 1, which were used in the studies that follow:

TABLE 1

	Female case	Female control
Pool size (Number)	335	335
Pool Criteria (ex: case/control)	control	case
Mean Age (ex: years)	57.21	69.95

Example 2

Association of Polymorphic Variants with Osteoarthritis

[0221] A whole-genome screen was performed to identify particular SNPs associated with occurrence of osteoarthritis. As described in Example 1, two sets of samples were utilized, which included samples from female individuals having knee osteoarthritis (osteoarthritis cases), and samples from female individuals not having knee osteoarthritis (female controls). The initial screen of each pool was performed in an allelotyping study, in which certain samples in each group were pooled. By pooling DNA from each group, an allele frequency for each SNP in each group was calculated. These allele frequencies were then compared to one another. Particular SNPs were considered as being associated with osteoarthritis when allele frequency differences calculated between case and control pools were statistically significant. SNP disease association results obtained from the allelotyping study were then validated by genotyping each associated SNP across all samples from each pool. The results of the genotyping then were analyzed, allele frequencies for each group were calculated from the individual genotyping results, and a p-value was calculated to determine whether the case and control groups had statistically significant differences in allele frequencies for a particular SNP. When the genotyping results agreed with the original allelotyping results, the SNP disease association was considered validated at the genetic level.

SNP Panel Used for Genetic Analyses

[0222] A whole-genome SNP screen began with an initial screen of approximately 25,000 SNPs over each set of disease and control samples using a pooling approach. The pools studied in the screen are described in Example 1. The SNPs analyzed in this study were part of a set of 25,488 SNPs confirmed as being statistically polymorphic as each is characterized as having a minor allele frequency of greater than 10%. The SNPs in the set reside in genes or in close proximity to genes, and many reside in gene exons. Specifically, SNPs in the set are located in exons, introns, and within 5,000 base-pairs upstream of a transcription start site of a gene. In addition, SNPs were selected according to the following criteria: they are located in ESTs; they are located in Locuslink or Ensembl genes; and they

are located in Genomatix promoter predictions. SNPs in the set were also selected on the basis of even spacing across the genome, as depicted in Table 2.

[0223] A case-control study design using a whole genome association strategy involving approximately 28,000 single nucleotide polymorphisms (SNPs) was employed. Approximately 25,000 SNPs were evenly spaced in gene-based regions of the human genome with a median inter-marker distance of about 40,000 base pairs. Additionally, approximately 3,000 SNPs causing amino acid substitutions in genes described in the literature as candidates for various diseases were used. The case-control study samples were of female Caucasian origin (British paternal and maternal descent) 670 individuals were equally distributed in two groups: female controls and female cases. The whole genome association approach was first conducted on 2 DNA pools representing the 2 groups. Significant markers were confirmed by individual genotyping.

TABLE 2

<u>General Statistics</u>		<u>Spacing Statistics</u>	
Total # of SNPs	25,488	Median	37,058 bp
# of Exonic SNPs	>4,335 (17%)	Minimum*	1,000 bp
# SNPs with refSNP ID	20,776 (81%)	Maximum*	3,000,000 bp
Gene Coverage	>10,000	Mean	122,412 bp
Chromosome Coverage	All	Std Deviation	373,325 bp
		<i>*Excludes outliers</i>	

Allelotyping and Genotyping Results

[0224] The genetic studies summarized above and described in more detail below identified allelic variants associated with osteoarthritis, which are summarized in Table B.

Assay for Verifying, Allelotyping, and Genotyping SNPs

[0225] A MassARRAY™ system (Sequenom, Inc.) was utilized to perform SNP genotyping in a high-throughput fashion. This genotyping platform was complemented by a homogeneous, single-tube assay method (hME™ or homogeneous MassEXTEND™ (Sequenom, Inc.)) in which two genotyping primers anneal to and amplify a genomic target surrounding a polymorphic site of interest. A third primer (the MassEXTEND™ primer), which is complementary to the amplified target up to but not including the polymorphism, was then enzymatically extended one or a few bases through the polymorphic site and then terminated.

[0226] For each polymorphism, SpectroDESIGNER™ software (Sequenom, Inc.) was used to generate a set of PCR primers and a MassEXTEND™ primer which were used to genotype the polymorphism. Other primer design software could be used or one of ordinary skill in the art could manually design primers based on his or her knowledge of the relevant factors and considerations in designing such primers. Table 3 shows PCR primers and Table 4 shows extension primers used for analyzing polymorphisms. The initial PCR amplification reaction was performed in a 5 µl total volume

containing 1X PCR buffer with 1.5 mM MgCl₂ (Qiagen), 200 μ M each of dATP, dGTP, dCTP, dTTP (Gibco-BRL), 2.5 ng of genomic DNA, 0.1 units of HotStar DNA polymerase (Qiagen), and 200 nM each of forward and reverse PCR primers specific for the polymorphic region of interest.

TABLE 3: PCR Primers

SNP Reference	Forward PCR primer	Reverse PCR primer
rs910223	ACGTTGGATGACAGAGTGTCAGGGCTCAGA	ACGTTGGATGTGGTTTTTCCAGTGTCTTAC
rs1367117	ACGTTGGATGTTGGTTTTCTTCAGCAAGGC	ACGTTGGATGAGCTTCATCCTGAAGACCAG
rs1024791	ACGTTGGATGGTGTAAAGGACTGCAGATAC	ACGTTGGATGAAACAGAACCAGGAGGTTGG
rs1041973	ACGTTGGATGGGGACTTCTGACAATACAGG	ACGTTGGATGAATCGTGTGTTTGCCTCAGG
rs1465621	ACGTTGGATGTTCTCCTCCCATTCTTCCTG	ACGTTGGATGGCGGGACTAGAAGTAGATTG
rs398829	ACGTTGGATGTAGTCATCGTCCGCAGCATG	ACGTTGGATGAAGACGGTGTCTCTCCTTG
rs1018810	ACGTTGGATGTGCTGCTCCCATTCTCATG	ACGTTGGATGAAGGAGTAGAGACCTTGCTG
rs1484086	ACGTTGGATGTGCTACTCTTCGGAAGTCTC	ACGTTGGATGCATGTACAGGGCATTACAG
rs242392	ACGTTGGATGTGTTTGGGCTGCTGTGGCTCT	ACGTTGGATGACCACTTCTCACGGTTACTG
rs8818	ACGTTGGATGAATCTCTCCCCTTCCAAAGC	ACGTTGGATGTCCCTGTGGTTTTTCATCCAC
rs1395486	ACGTTGGATGCTCATTTATTTTCATGTTTAC	ACGTTGGATGTGCTGGAATAATGATTGTTG
rs512294	ACGTTGGATGTCTTGCTACCCACCTCCGAG	ACGTTGGATGAGAGCTCATGAGGGAATGGG
rs132659	ACGTTGGATGGGCCCATAGTGGGTCATAAC	ACGTTGGATGGTGGGGTGAGTGCCCAAAG

[0227] Samples were incubated at 95°C for 15 minutes, followed by 45 cycles of 95°C for 20 seconds, 56°C for 30 seconds, and 72°C for 1 minute, finishing with a 3 minute final extension at 72°C. Following amplification, shrimp alkaline phosphatase (SAP) (0.3 units in a 2 μ l volume) (Amersham Pharmacia) was added to each reaction (total reaction volume was 7 μ l) to remove any residual dNTPs that were not consumed in the PCR step. Samples were incubated for 20 minutes at 37°C, followed by 5 minutes at 85°C to denature the SAP.

[0228] Once the SAP reaction was complete, a primer extension reaction was initiated by adding a polymorphism-specific MassEXTEND™ primer cocktail to each sample. Each MassEXTEND™ cocktail included a specific combination of dideoxynucleotides (ddNTPs) and deoxynucleotides (dNTPs) used to distinguish polymorphic alleles from one another. Methods for verifying, allelotyping and genotyping SNPs are disclosed, for example, in U.S. Pat. No. 6,258,538, the content of which is hereby incorporated by reference. In Table 4, ddNTPs are shown and the fourth nucleotide not shown is the dNTP.

TABLE 4: Extension Primers

SNP Reference	Extend Probe	Termination Mix
rs910223	GGGTCTGCACTG GTCCCA	ACT
rs1367117	AGCCATACACCTC TTTTCAAGG	ACT
rs1024791	CTGGCTGATGTCA GAAAGCA	ACG
rs1041973	ATACCAGAATCA GCAACT	ACT
rs1465621	CCATTCTTCCTGACATTGCGC	CGT
rs398829	TGGCGTGCTCCTCTAGGA	ACG
rs1018810	CTGCTTTTATACATGCCACAC	ACT
rs1484086	CTCTTCGGAAGTCTCTTTCTCA	ACT
rs242392	CTGCTGTGGCTCTACTGGT	ACG

SNP Reference	Extend Probe	Termination Mix
rs8818	AGCCCCCAACCCACAGGCA	ACT
rs1395486	TTTCATGTTCAAAAAATCTTCT	ACG
rs512294	AGCTGGAGAGCAAACCACC	ACT
rs132659	AGAACTCCC CAAATCGTCCT	ACG

[0229] The MassEXTEND™ reaction was performed in a total volume of 9 µl, with the addition of 1X ThermoSequenase buffer, 0.576 units of ThermoSequenase (Amersham Pharmacia), 600 nM MassEXTEND™ primer, 2 mM of ddATP and/or ddCTP and/or ddGTP and/or ddTTP, and 2 mM of dATP or dCTP or dGTP or dTTP. The deoxy nucleotide (dNTP) used in the assay normally was complementary to the nucleotide at the polymorphic site in the amplicon. Samples were incubated at 94°C for 2 minutes, followed by 55 cycles of 5 seconds at 94°C, 5 seconds at 52°C, and 5 seconds at 72°C.

[0230] Following incubation, samples were desalted by adding 16 µl of water (total reaction volume was 25 µl), 3 mg of SpectroCLEAN™ sample cleaning beads (Sequenom, Inc.) and allowed to incubate for 3 minutes with rotation. Samples were then robotically dispensed using a piezoelectric dispensing device (SpectroJET™ (Sequenom, Inc.)) onto either 96-spot or 384-spot silicon chips containing a matrix that crystallized each sample (SpectroCHIP™ (Sequenom, Inc.)). Subsequently, MALDI-TOF mass spectrometry (Biflex and Autoflex MALDI-TOF mass spectrometers (Bruker Daltonics) can be used) and SpectroTYPER RT™ software (Sequenom, Inc.) were used to analyze and interpret the SNP genotype for each sample.

Genetic Analysis

[0231] Minor allelic frequencies for the polymorphisms set forth in Table B were verified as being 10% or greater using the extension assay described above in a group of samples isolated from 92 individuals originating from the state of Utah in the United States, Venezuela and France (Coriell cell repositories).

[0232] Genotyping results are shown for female pools in Table 5. In Table 5, “AF” refers to allelic frequency; and “F case” and “F control” refer to female case and female control groups, respectively.

TABLE 5: Genotyping Results

SNP Reference	AF F case	AF F control	p-value
rs910223	A = 0.148 G = 0.852	A = 0.099 G = 0.901	0.0069
rs1367117	A = 0.339 G = 0.661	A = 0.402 G = 0.598	0.0181
rs1024791	G = 0.129 A = 0.871	G = 0.088 A = 0.912	0.0158
rs1041973	A = 0.189 C = 0.811	A = 0.233 C = 0.767	0.0539
rs1465621	T = 0.071 A = 0.929	T = 0.107 A = 0.893	0.0194
rs398829	G = 0.740	G = 0.652	0.0002

	A = 0.260	A = 0.348	
rs1018810	A = 0.142 G = 0.858	A = 0.094 G = 0.906	0.0063
rs1484086	T = 0.821 C = 0.179	T = 0.753 C = 0.247	0.0027
rs242392	C = 0.100 T = 0.900	C = 0.139 T = 0.861	0.0272
rs8818	G = 0.158 C = 0.842	G = 0.213 C = 0.787	0.0105
rs1395486	C = 0.115 T = 0.885	C = 0.158 T = 0.842	0.0231
rs512294	A = 0.078 G = 0.922	A = 0.124 G = 0.876	0.0054
rs132659	C = 0.675 T = 0.325	C = 0.589 T = 0.411	0.0015

[0233] All of the single marker alleles set forth in Table B were considered validated, since the genotyping data agreed with the allelotyping data and each SNP significantly associated with osteoarthritis. Particularly significant associations with osteoarthritis are indicated by a calculated p-value of less than 0.05 for genotype results.

Example 3

Association of Polymorphic Variants with Osteoarthritis in Replication Cohorts

[0234] The single marker polymorphisms set forth in Table B were genotyped again in two replication cohorts consisting of individuals selected for OA.

Sample Selection and Pooling Strategies – Replication Sample 1

[0235] A second case control sample (replication sample #1) was created by using 100 Caucasian female cases from Chingford, UK, and 148 unrelated female cases from the St. Thomas twin study. Cases were defined as having Kellgren-Lawrence (KL) scores of at least 2 in at least one knee x-ray. In addition, 199 male knee replacement cases from Nottingham were included. (For a cohort description, see the Nottingham description provided in Example 1). The control pool was made up of unrelated female individuals from the St. Thomas twin study (England) with normal knee x-rays and without other indications of OA, regardless of anatomical location, as well as lacking family history of OA. The St. Thomas twin study consists of Caucasian, female participants from the St. Thomas' Hospital, London, adult-twin registry, which is a voluntary registry of >4,000 twin pairs ranging from 18 to 76 years of age. The replication sample 1 cohort was used to replicate the initial results. Table 6 below summarizes the selected phenotype data collected from the case and control individuals.

TABLE 6

Phenotype	Female cases (n=248): median (range)/ (n,%)	Male cases (n=199): median (range)/ (n,%)	Female controls (n=313): mean (range)/ (n,%)
Age	59 (39- 73)	66 (45- 73)	55 (50- 72)
Height (cm)	162 (141- 178)	175 (152- 198)	162 (141- 176)

Phenotype	Female cases (n=248): median (range)/ (n,%)	Male cases (n=199): median (range)/ (n,%)	Female controls (n=313): mean (range)/ (n,%)
Weight (kg)	68 (51- 123)	86 (62- 127)	64 (40- 111)
Body mass index (kg/m ²)	26 (18- 44)	29 (21- 41)	24 (18- 46)
Kellgren- Lawrence* left knee	0 (63, 26%), 1 (20, 8%), 2 (105, 43%), 3 (58, 23%), 4 (1, 0%)	NA	NA
Kellgren- Lawrence* right knee	0 (43, 7%), 1 (18, 7%), 2 (127, 52%), 3 (57, 23%), 4 (1, 0%)	NA	NA
KL* >2 both knees	No (145, 59%), Yes (101, 41%)	NA	NA
KL* >2 either knee	No (0, 0%), Yes (248, 100%)	NA	NA

* 0: normal, 1: doubtful, 2: definite osteophyte (bony protuberance), 3: joint space narrowing (with or without osteophyte), 4: joint deformity

Sample Selection and Pooling Strategies – Replication Sample 2

[0236] A third case control sample (replication sample #2) was created by using individuals with symptoms of OA from Newfoundland, Canada. These individuals were recruited and examined by theumatologists. Affected joints were x-rayed and a final diagnosis of definite or probable OA was made according to American College of Rheumatology criteria by a single rheumatologist to avoid any inter-examiner diagnosis variability. Controls were recruited from volunteers without any symptoms from the musculoskeletal system based on a normal joint exam performed by a rheumatologist. Only cases with a diagnosis of definite OA were included in the study. Only individuals of Caucasian origin were included. The cases consisted of 228 individuals with definite knee OA, 106 individuals with definite hip OA, and 74 individuals with hip OA.

TABLE 7

Phenotype	Case	Control
Age at Visit	62.7	52.5
Sex (Female/Male)	227/119	174/101
Knee OA Xray: No	35% (120)	80% (16)
Unknown	1% (4)	0% (0)
Yes	64% (221)	20% (4)
Hip OA Xray: No	63% (215)	80% (16)
Unknown	2% (7)	0% (0)
Yes	35% (121)	20% (4)

Assay for Verifying, Allelotyping, and Genotyping SNPs

[0237] Genotyping of the replication cohorts described in Tables 6 and 7 was performed using the same methods used for the original genotyping, as described herein. A MassARRAY™ system

(Sequenom, Inc.) was utilized to perform SNP genotyping in a high-throughput fashion. This genotyping platform was complemented by a homogeneous, single-tube assay method (hME™ or homogeneous MassEXTEND™ (Sequenom, Inc.)) in which two genotyping primers anneal to and amplify a genomic target surrounding a polymorphic site of interest. A third primer (the MassEXTEND™ primer), which is complementary to the amplified target up to but not including the polymorphism, was then enzymatically extended one or a few bases through the polymorphic site and then terminated.

[0238] For each polymorphism, SpectroDESIGNER™ software (Sequenom, Inc.) was used to generate a set of PCR primers and a MassEXTEND™ primer which were used to genotype the polymorphism. Other primer design software could be used or one of ordinary skill in the art could manually design primers based on his or her knowledge of the relevant factors and considerations in designing such primers. Table 3 shows PCR primers and Table 4 shows extension probes used for analyzing (*e.g.*, genotyping) polymorphisms in the replication cohorts. The initial PCR amplification reaction was performed in a 5 µl total volume containing 1X PCR buffer with 1.5 mM MgCl₂ (Qiagen), 200 µM each of dATP, dGTP, dCTP, dTTP (Gibco-BRL), 2.5 ng of genomic DNA, 0.1 units of HotStar DNA polymerase (Qiagen), and 200 nM each of forward and reverse PCR primers specific for the polymorphic region of interest.

[0239] Samples were incubated at 95°C for 15 minutes, followed by 45 cycles of 95°C for 20 seconds, 56°C for 30 seconds, and 72°C for 1 minute, finishing with a 3 minute final extension at 72°C. Following amplification, shrimp alkaline phosphatase (SAP) (0.3 units in a 2 µl volume) (Amersham Pharmacia) was added to each reaction (total reaction volume was 7 µl) to remove any residual dNTPs that were not consumed in the PCR step. Samples were incubated for 20 minutes at 37°C, followed by 5 minutes at 85°C to denature the SAP.

[0240] Once the SAP reaction was complete, a primer extension reaction was initiated by adding a polymorphism-specific MassEXTEND™ primer cocktail to each sample. Each MassEXTEND™ cocktail included a specific combination of dideoxynucleotides (ddNTPs) and deoxynucleotides (dNTPs) used to distinguish polymorphic alleles from one another. Methods for verifying, allelotyping and genotyping SNPs are disclosed, for example, in U.S. Pat. No. 6,258,538, the content of which is hereby incorporated by reference. In Table 7, ddNTPs are shown and the fourth nucleotide not shown is the dNTP.

[0241] The MassEXTEND™ reaction was performed in a total volume of 9 µl, with the addition of 1X ThermoSequenase buffer, 0.576 units of ThermoSequenase (Amersham Pharmacia), 600 nM MassEXTEND™ primer, 2 mM of ddATP and/or ddCTP and/or ddGTP and/or ddTTP, and 2 mM of dATP or dCTP or dGTP or dTTP. The deoxy nucleotide (dNTP) used in the assay normally was complementary to the nucleotide at the polymorphic site in the amplicon. Samples were incubated at 94°C for 2 minutes, followed by 55 cycles of 5 seconds at 94°C, 5 seconds at 52°C, and 5 seconds at 72°C.

[0242] Following incubation, samples were desalted by adding 16 μ l of water (total reaction volume was 25 μ l), 3 mg of SpectroCLEAN™ sample cleaning beads (Sequenom, Inc.) and allowed to incubate for 3 minutes with rotation. Samples were then robotically dispensed using a piezoelectric dispensing device (SpectroJET™ (Sequenom, Inc.)) onto either 96-spot or 384-spot silicon chips containing a matrix that crystallized each sample (SpectroCHIP™ (Sequenom, Inc.)). Subsequently, MALDI-TOF mass spectrometry (Biflex and Autoflex MALDI-TOF mass spectrometers (Bruker Daltonics) can be used) and SpectroTYPER RT™ software (Sequenom, Inc.) were used to analyze and interpret the SNP genotype for each sample.

Genetic Analysis

[0243] Genotyping results for replication cohorts #1 and #2 are provided in Tables 8 and 9, respectively.

TABLE 8

rsID	Replication #1 (Mixed Male/Female cases and Female controls)				Meta-analysis Disc. + Rep #1
	AF OA Con	AF OA Cas	Delta	P-value	P-value
rs910223	0.87	0.86	0.01	0.650	0.1800
rs1367117	0.67	0.64	0.03	0.182	0.9900
rs1024791	0.87	0.87	-0.01	0.718	0.5900
rs1041973	0.77	0.79	-0.02	0.357	Not calculated
rs1465621	0.89	0.91	-0.02	0.209	0.0095
rs398829	0.30	0.28	0.02	0.307	0.0260
rs1018810	0.91	0.89	0.02	0.289	0.0062
rs1484086	0.23	0.20	0.03	0.287	0.0077
rs242392	0.87	0.87	0.00	0.927	0.2400
rs8818	0.78	0.81	-0.03	0.259	0.0150
rs1395486	0.87	0.88	-0.01	0.492	0.0390
rs512294	0.89	0.88	0.00	0.909	0.3600
rs132659	0.38	0.34	0.04	0.128	0.0077

TABLE 9

rsID	Replication #2 (Newfoundland) (Male/Female cases and controls)				Meta-analysis Disc. + Rep #2
	AF OA Con	AF OA Cas	Delta	P-value	Not Done
rs910223	0.86	0.86	0.001	0.974	
rs1367117	0.64	0.69	-0.049	0.081	
rs1024791	0.87	0.87	0.006	0.767	
rs1041973	0.78	0.79	-0.016	0.510	
rs1465621	0.92	0.92	0.003	0.837	
rs398829	0.27	0.28	-0.013	0.627	
rs1018810					
rs1484086	0.23	0.21	0.026	0.280	
rs242392	0.88	0.88	-0.005	0.813	

rsID	Replication #2 (Newfoundland) (Male/Female cases and controls)				Meta-analysis Disc. + Rep #2 Not Done
	AF OA Con	AF OA Cas	Delta	P-value	
rs8818	0.85	0.82	0.034	0.127	
rs1395486	0.86	0.85	0.015	0.486	
rs512294	0.90	0.93	-0.037	0.021	
rs132659	0.36	0.36	-0.001	0.973	

[0244] To combine the evidence for association from multiple sample collections, a meta-analysis procedure was employed. The allele frequencies were compared between cases and controls within the discovery sample, as well as within the replication cohort #1 using the DerSimonian-Laird approach (DerSimonian, R. and N. Laird. 1986. Meta-analysis in clinical trials. *Control Clin Trials* 7: 177-188.)

[0245] The absence of a statistically significant association in one or more of the replication cohorts should not be interpreted as minimizing the value of the original finding. There are many reasons why a biologically derived association identified in a sample from one population would not replicate in a sample from another population. The most important reason is differences in population history. Due to bottlenecks and founder effects, there may be common disease predisposing alleles present in one population that are relatively rare in another, leading to a lack of association in the candidate region. Also, because common diseases such as arthritis-related disorders are the result of susceptibilities in many genes and many environmental risk factors, differences in population-specific genetic and environmental backgrounds could mask the effects of a biologically relevant allele. For these and other reasons, statistically strong results in the original, discovery sample that did not replicate in one or more of the replication samples may be further evaluated in additional replication cohorts and experimental systems.

[0246] *APOB*, *IL1RL2*, *WASPI*, *BVES*, *LOXLI* and *CASPR4* regions were analyzed further, as shown in the examples below. *PADI2*, described above, is a peptidyl arginine deiminase enzyme, type II, that converts arginine residues within proteins to citrulline residues. This gene is one of four known *PADI* genes that encode enzymes that catalyze conversion of arginine to citrulline in proteins. Individuals with rheumatoid arthritis (RA) frequently have autoantibodies to citrullinated peptides, suggesting the involvement of the peptidylarginine deiminases citrullinating enzymes in RA (van Venrooij et al., *Arthritis Res.*;2(4):249-51. Epub 2000 May 24).

[0247] Pellino homolog 2 from *Drosophila* (*PELI2*) is a member of the Pellino gene family, which are involved in Toll-like signalling pathways. Pellino-2 associates with the pelle-like kinase/IL-1R-associated kinase protein to couple the pelle-like kinase/IL-1R-associated kinase protein to IL-1- or LPS-dependent signaling. *PELI2* may act as a downstream effector of interleukin receptor signaling and may play a role in inflammation-mediated Osteoarthritis. Pathway members downstream of *PELI2* may be targetable (e.g., interleukin receptors).

[0248] G protein-coupled receptor 50 (*GPR50*) is a member of the G protein-coupled receptor family. *GPR50* has significant homology to melatonin receptors and was isolated by PCR of human genomic DNA with degenerate primers based on conserved regions of melatonin receptors.

Example 4

APOB Proximal SNPs

[0249] It has been discovered that rs1367117 is associated with occurrence of osteoarthritis in subjects. The polymorphic variant lies within the *APOB* gene and codes for a I98T amino acid change. The guanine allele of SNP rs1367117 is associated with osteoarthritis (see Table 5) and codes for a threonine at position 98 (see, for example, amino acid sequence in SEQ ID NO: 38).

[0250] Apolipoprotein B (*ApoB*) is the main apolipoprotein of chylomicrons and low density lipoproteins (LDL). *ApoB* binds to sulfated proteoglycans, especially chondroitin and dermatan sulfate, that are components of cartilage (Camejo et. al., *Atherosclerosis*. 1998 Aug;139(2):205-22). This may contribute to inflammation/joint damage by lipoprotein oxidation products. In addition, increased levels of *ApoB* is seen as a risk factor for osteonecrosis (Miyamishi et. al., *Ann Rheum Dis*. 1999 Aug;58(8):514-6). Lipoprotein deposition has been noted in inflammatory (rheumatoid) arthritis and may play a role in inflammation mediated osteoarthritis. *ApoB* function can be modulated by addition of an antibody or a decoy receptor for *ApoB*. Examples of antibodies and small molecules that specifically interact with *ApoB* are described in U.S. Patent Nos. 6,107,045; 6,309,844; 5,330,910; and 6,369,075.

[0251] One hundred twenty-two additional allelic variants proximal to rs1367117 were identified and subsequently allelotyped in osteoarthritis case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 10. The chromosome positions provided in column four of Table 10 are based on Genome "Build 34" of NCBI's GenBank.

TABLE 10

dbSNP rs#	Chromosome	Position in SEQ ID NO: 2	Chromosome Position	Allele Variants
rs1318006	2	238	21188688	C/T
rs1318005	2	294	21188744	C/T
rs1318004	2	295	21188745	A/G
rs1318003	2	347	21188797	A/C
rs4327259	2	1425	21189875	A/C
rs6756501	2	4891	21193341	C/T
rs6725189	2	5087	21193537	G/T
rs4665709	2	7041	21195491	A/G
rs4665710	2	7121	21195571	A/C
rs4371387	2	7219	21195669	A/G
rs952274	2	7443	21195893	G/T
rs952275	2	7485	21195935	G/T
rs1801695	2	10939	21199389	A/G
rs1042034	2	11367	21199817	A/G
rs1801702	2	11571	21200021	C/G

dbSNP rs#	Chromosome	Position in SEQ ID NO: 2	Chromosome Position	Allele Variants
rs1042031	2	11839	21200289	A/G
rs2678378	2	12551	21201001	A/G
rs2678379	2	12646	21201096	A/G
rs1800479	2	13469	21201919	G/C
rs1801701	2	14913	21203363	A/G
rs4362589	2	15205	21203655	G/T
rs5742904	2	15246	21203696	A/G
rs1799812	2	15695	21204145	G/A
rs2163204	2	17473	21205923	G/T
rs676210	2	17610	21206060	A/G
rs1042006	2	17828	21206278	A/C
rs1801696	2	18130	21206580	A/G
rs693	2	18281	21206731	C/T
rs1041974	2	18623	21207073	C/G
rs1041968	2	18890	21207340	C/T
rs568413	2	21561	21210011	C/T
rs2854726	2	23100	21211550	A/T
rs2854725	2	23872	21212322	A/C
rs2000998	2	24581	21213031	A/T
rs2000997	2	24582	21213032	A/T
rs497166	2	24983	21213433	C/T
rs562956	2	27540	21215990	A/T
rs7589300	2	30846	21219296	C/T
rs3791980	2	31415	21219865	G/T
rs3791981	2	31453	21219903	A/G
rs1801700	2	31899	21220349	T/C
rs679899	2	37000	21225450	A/G
rs1041952	2	38681	21227131	C/G
rs6727706	2	39287	21227737	C/T
rs6719207	2	42951	21231401	A/T
rs1469513	2	45648	21234098	C/T
rs1800478	2	46222	21234672	C/T
rs550619	2	46687	21235137	A/G
rs6752026	2	47020	21235470	A/G
rs579826	2	47593	21236043	C/T
rs597331	2	48513	21236963	C/T
rs1367116	2	49723	21238173	A/G
rs1367117	2	49986	21238436	A/G
rs1800480	2	53018	21241468	C/G
rs1800481	2	53296	21241746	C/T
rs934197	2	53547	21241997	A/G
rs1625764	2	53899	21242349	C/T
rs1625714	2	53916	21242366	G/T
rs1560357	2	53933	21242383	A/C
rs617314	2	54305	21242755	G/T
rs547186	2	55327	21243777	A/T
rs589566	2	55895	21244345	C/T
rs588245	2	56143	21244593	C/T
rs585967	2	56640	21245090	G/T
rs7562777	2	58486	21246936	A/G
rs7575840	2	59576	21248026	G/T
rs7567653	2	63048	21251498	A/G

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 2	Chromosome Position	Allele Variants
rs6548010	2	64008	21252458	A/G
rs6548011	2	64018	21252468	C/T
rs934198	2	64859	21253309	A/C
rs634292	2	65995	21254445	G/T
rs1003177	2	66905	21255355	A/G
rs6726115	2	67183	21255633	A/G
rs481069	2	67942	21256392	C/T
rs1367115	2	68101	21256551	A/G
rs666126	2	68521	21256971	A/G
rs7566030	2	68664	21257114	C/G
rs7590135	2	68988	21257438	A/G
rs6718513	2	69178	21257628	C/G
rs515135	2	72143	21260593	A/G
rs1367114	2	74183	21262633	C/G
rs563290	2	74312	21262762	C/T
rs562338	2	74407	21262857	C/T
rs581411	2	75518	21263968	A/G
rs580889	2	76153	21264603	A/G
rs548145	2	77398	21265848	A/G
rs668948	2	77615	21266065	A/G
rs594677	2	79092	21267542	C/T
rs571468	2	80000	21268450	G/T
rs4665492	2	80125	21268575	A/C
rs622236	2	80595	21269045	G/T
rs541041	2	81061	21269511	C/T
rs540156	2	81151	21269601	A/G
rs1367113	2	81918	21270368	C/T
rs1897084	2	83072	21271522	C/T
rs1897083	2	83137	21271587	C/T
rs478588	2	83235	21271685	C/T
rs664894	2	83263	21271713	A/T
rs1594286	2	83279	21271729	A/G
rs7422168	2	83280	21271730	C/G
rs565202	2	83533	21271983	C/T
rs1429974	2	86856	21275306	G/T
rs5829769	2	87186	21275636	-/TATA
rs3056575	2	87189	21275639	-/ATAT
rs6708168	2	87727	21276177	A/T
rs6756743	2	87978	21276428	C/T
rs2195598	2	89129	21277579	A/G
rs7567217	2	89556	21278006	C/T
rs568938	2	89702	21278152	A/G
rs666416	2	90233	21278683	A/G
rs6761300	2	93060	21281510	A/G
rs5829770	2	94779	21283229	-/T
rs1429973	2	95367	21283817	A/G
rs1429972	2	95844	21284294	A/G
rs6756284	2	95942	21284392	A/G
rs749988	2	96884	21285334	C/T
rs749987	2	96938	21285388	A/G
rs754524	2	97627	21286077	A/C
rs754523	2	97777	21286227	C/T

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 2	Chromosome Position	Allele Variants
rs675430	2	97871	21286321	A/C
rs600012	2	98746	21287196	A/G
rs614303	2	99663	21288113	A/G

Assay for Verifying and Allelotyping SNPs

[0252] The methods used to verify and allelotype the 122 proximal SNPs of Table 10 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 11 and Table 12, respectively.

TABLE 11

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs1318006	ACGTTGGATGTCTCATGGCCCATCCAAGGC	ACGTTGGATGAAGGAGCCCATGAAGGCAGC
rs1318005	ACGTTGGATGACAGCCTTGGATGGGCCATG	ACGTTGGATGTCTCCCAGTCTGGTGGAAAG
rs1318004	ACGTTGGATGACAGCCTTGGATGGGCCATG	ACGTTGGATGTCTCCCAGTCTGGTGGAAAG
rs1318003	ACGTTGGATGTTTCCACCAGACTGGGAGAC	ACGTTGGATGAGTGCCCAGCACAGAGTCTT
rs4327259	ACGTTGGATGAACAAGCTTGCTCAGCCACT	ACGTTGGATGTGTGTTCTGTCCAGGAAGAG
rs6756501	ACGTTGGATGATGCATTTCATTGCTGTTTG	ACGTTGGATGGAGATCAATGAGAAAAATAGG
rs6725189	ACGTTGGATGAAGAACAATAGAGAGGGCCG	ACGTTGGATGAGTATTGACTGCCTTGGTTC
rs4665709	ACGTTGGATGGCACAACCTCATAGATGTGG	ACGTTGGATGCCACCTCCATCATTGTGGAT
rs4665710	ACGTTGGATGAATCCACAATGATGGAGGTG	ACGTTGGATGGATAACTCACTCACTATCACG
rs4371387	ACGTTGGATGTAAAAGTGTGTAGCACCTCC	ACGTTGGATGTCATGGCAGAAAGTTAAAGGG
rs952274	ACGTTGGATGCAGAAGGGTGACATGCATTG	ACGTTGGATGCTCATATCCAGATTCACCCC
rs952275	ACGTTGGATGCACAATGCATGTCACCCTTC	ACGTTGGATGGACACTCTCTTTGCTGAAGG
rs1801695	ACGTTGGATGGAAATTATTTCTTCGTCG	ACGTTGGATGTGCTCAGGAAATAATTAAA
rs1042034	ACGTTGGATGATCCAAGATGAGATCAACAC	ACGTTGGATGGGCATAGGTTTTCTTTCAAC
rs1801702	ACGTTGGATGTTTTGATAAATCTTTCAAC	ACGTTGGATGCTAATAGATGTAATCTCGA
rs1042031	ACGTTGGATGGTTTGATGGCTTGGTACGAG	ACGTTGGATGTTTCCCCGGAAACTGGAATC
rs2678378	ACGTTGGATGGTTTTAGTCTTAGGAAGGC	ACGTTGGATGTATCACATGCCCCAGAAAGG
rs2678379	ACGTTGGATGCTTCCTAGGACTGAAAAGTG	ACGTTGGATGTGGGCTCCAACCTTGCCTTTT
rs1800479	ACGTTGGATGAAGGGTATGGAGATGAAGA	ACGTTGGATGACCTTATACCTTTTGAAA
rs1801701	ACGTTGGATGCTTGGTCATTGGAAAGCTCG	ACGTTGGATGGTGGCCCTGAATGCTAACAC
rs4362589	ACGTTGGATGCTGCAGGGCACTTCCAAAT	ACGTTGGATGTATATGCGTTGGAGTGTGGC
rs5742904	ACGTTGGATGATTTTGAAGTGCCCTGCAG	ACGTTGGATGCTATTGCTAGTGAGGCCAAC
rs1799812	ACGTTGGATGTTGTGGTGCCCTCTAATTT	ACGTTGGATGCATCTTCATCTGTCATTGA
rs2163204	ACGTTGGATGTTTGGACTCTCCTTTGGCAG	ACGTTGGATGGCTGACATAGGGAATGGAAC
rs676210	ACGTTGGATGCCCAACTCTCAACCTTAATG	ACGTTGGATGAATTGTGTGTGAGATGTGGG
rs1042006	ACGTTGGATGCAGCATCTGGTCAATGGTTC	ACGTTGGATGACACCTTCCACATTCTTCC
rs1801696	ACGTTGGATGTGCTAAGAACCTTACTGAC	ACGTTGGATGGCCCAATCTTGATAGAAT
rs693	ACGTTGGATGCAGCATCTTTGGCTCACATG	ACGTTGGATGTCCTGCTGAATGTCCATTG
rs1041974	ACGTTGGATGTACTTTGAGAAATTGGTTGG	ACGTTGGATGGTTAACATCTTCAATGAATG
rs1041968	ACGTTGGATGTCAGCTACTTCAAAATCCCC	ACGTTGGATGGGCTATTGATGTTAGAGTGC
rs568413	ACGTTGGATGGAGACTGGGTTGTTTCCAAG	ACGTTGGATGCCACAAGAATACGTTACAC
rs2854726	ACGTTGGATGCTCTAGCTTAACAGCAAGCC	ACGTTGGATGGCAAATCTCCCTCTGACTG
rs2854725	ACGTTGGATGCATTCAGCTTTGTGTAAGTG	ACGTTGGATGTTTCCAAAGACTGTATAAGG
rs2000998	ACGTTGGATGTGAACCATCCTTGATCTGG	ACGTTGGATGTGGCACCAATGATTTTGTCC
rs2000997	ACGTTGGATGTGGCACCAATGATTTTGTCC	ACGTTGGATGTGAACCATCCTTGATCTGG
rs497166	ACGTTGGATGTCCCAAAGTGCTGGGATTAC	ACGTTGGATGAAATCCAACCTGGACATGCGC
rs562956	ACGTTGGATGTAACAGTCTTACCACACGGC	ACGTTGGATGATAAGGGAAAGTCTCCCTGG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs7589300	ACGTTGGATGTACCACGTATGTTGAGTGAG	ACGTTGGA TGCCCTTACTCTATGATTACTGC
rs3791980	ACGTTGGATGTCTGGAGAGATCATCTTTGG	ACGTTGGA TGCTACCTAGCTACCTCAAATC
rs3791981	ACGTTGGATGTGTTTTGAGAATGAAGAAAC	ACGTTGGA TGGGTCTTAGGTATTTTTTGGG
rs1801700	ACGTTGGATGGACCCGACTCGTGGAAGAA	ACGTTGGA TGTCGCTAGGAGTGGGGTCCA
rs679899	ACGTTGGATGCTGAAGTCCATGACAGTTGG	ACGTTGGA TGTTGTGGCTTCCCATATTGCC
rs1041952	ACGTTGGATGCATGGAGCAGTTAACTCCAG	ACGTTGGA TGCTCTGGATCATCAGTGATGGC
rs6727706	ACGTTGGATGGCACCACCTTATTGAAAAGGG	ACGTTGGA TGACATACTTACAGTCAACGG
rs6719207	ACGTTGGATGGTCCCAGTTGTAACCATGTC	ACGTTGGA TGGGAATCCAGACTTGTCTGAG
rs1469513	ACGTTGGATGCTTTTCTGCACAAGGACTCC	ACGTTGGA TGACTCCACTTCATGGGATGAG
rs1800478	ACGTTGGATGTGACGGTAAAGTGAGTGAG	ACGTTGGA TGCCCGTGTGTAATACATGTGG
rs550619	ACGTTGGATGGCAAACACAGGTGAAGCATC	ACGTTGGA TGGGCTTATCAGGTTGGGTCTA
rs6752026	ACGTTGGATGCAGAAGGGAAGCAGGTTTTTC	ACGTTGGA TGCAAGAAATGATGCCCTCTTG
rs579826	ACGTTGGATGAAAGTGCTGGGACTACAGGC	ACGTTGGA TGATATGGGTGGAGAACAGAGC
rs597331	ACGTTGGATGACACTCTCTCAGAAAAGTTCC	ACGTTGGA TGGTATGGTGATCAGATCAGAG
rs1367116	ACGTTGGATGCAAGAAGTTTAAAGCATGAG	ACGTTGGA TGATCATCAAAAAGAGAGAAGC
rs1367117	ACGTTGGATGTTGGTTTTCTTCAGCAAGGC	ACGTTGGA TGAGCTTCATCCTGAAGACCAG
rs1800480	ACGTTGGATGCCGAGAAGGGCACTCAGCC	ACGTTGGA TGCGCCGGCCGCGCATTCCCA
rs1800481	ACGTTGGATGATCTGAAGAAGGCACCCCTG	ACGTTGGA TGAAGCGTCTTCAGTGCTCTGG
rs934197	ACGTTGGATGTGACTGGTCACTCACCAGAC	ACGTTGGA TGATCCTGATCAGAATCTGTGG
rs1625764	ACGTTGGATGCAGAGGCATCGAGCGCTGG	ACGTTGGA TGACAGGACACGTCATGTTCC
rs1625714	ACGTTGGATGAATTCCTACTACCGCTGATTC	ACGTTGGA TGATCGTTTCTCTCTCTTAG
rs1560357	ACGTTGGATGGTCCCTGAAATTCCTACTACC	ACGTTGGA TGATTCCACCGGAAGCTTCA
rs617314	ACGTTGGATGCAGTCTTCACCACTAGCTTG	ACGTTGGA TGTTGCAGAAGTCAGTGTGTGC
rs547186	ACGTTGGATGCAGTTCAGGGAAGACTTGCC	ACGTTGGA TGGAGAGGACTGTCACCATCTC
rs589566	ACGTTGGATGCCCAGCAGACCAATATTCTG	ACGTTGGA TGGGTATAGCTGAATGGTGCAG
rs588245	ACGTTGGATGGCTCCAAAATCTCATCTGGC	ACGTTGGA TGAGCTTCTGGGCATCATTTGC
rs585967	ACGTTGGATGTGACAGGGAATCAGAGTCAC	ACGTTGGA TGCCACCTACTGCACTGAATCT
rs7562777	ACGTTGGATGTTGGAGATTGCTCTTTGGGC	ACGTTGGA TGAGCTCAGGTTATCCACAC
rs7575840	ACGTTGGATGCATAGACTGTCCATCACAGG	ACGTTGGA TGGGTGTCAGAAAAACTTCCAC
rs7567653	ACGTTGGATGAAAGTGGTGATGGATGCCTG	ACGTTGGA TGGGGAGCAAATAGCTCATCTG
rs6548010	ACGTTGGATGGCCTGGATTCCGGGTTTTTAA	ACGTTGGA TGCTATAAGCTGCTTATCAGAG
rs6548011	ACGTTGGATGCTATAAGCTGCTTATCAGAG	ACGTTGGA TGGCCTGGATTCCGGTTTTTAA
rs934198	ACGTTGGATGACATGGAAGGAGGATGAGTG	ACGTTGGA TGAGGTAGGACCCTCATGATTG
rs634292	ACGTTGGATGGAGGCTTGTTTATGGCACAG	ACGTTGGA TGCGTGCTTTTTCTCAAGTGCC
rs1003177	ACGTTGGATGTACACAGACCCAGAAGATAC	ACGTTGGA TGATGCATGAACAAAGGAAGC
rs6726115	ACGTTGGATGATACAGATAAGGCACTTGGC	ACGTTGGA TGAGGGAAGTGAACGTGAAAGG
rs481069	ACGTTGGATGTTTGAACCTTCTGAATGGTG	ACGTTGGA TGATTGTGAGGGTTTACTTTCC
rs1367115	ACGTTGGATGGGTTTGAACAACTGATTGG	ACGTTGGA TGGGTAGGGAATACTTTCAACG
rs666126	ACGTTGGATGTTCTGCAGGATTCATCTCTC	ACGTTGGA GTTTTGTATGCCAGGTTAAGG
rs7566030	ACGTTGGATGGATACAGAAGAGAGTGGTGG	ACGTTGGA TGAGACTTGAGCCTTCAATGGC
rs7590135	ACGTTGGATGACTGGTCTTAGGGTTACACC	ACGTTGGA TGACAAAGCACCTGCTCCAAGA
rs6718513	ACGTTGGATGCTTCCCTAGGTCTGAAGAAC	ACGTTGGA TGGCTTCTTTAGTGCCAAAGAG
rs515135	ACGTTGGATGGGCTTACAGCCAAGTAACAG	ACGTTGGA TGACCATCTTGTACTGCACAG
rs1367114	ACGTTGGATGGTTGGAGAATTATTTGCAGG	ACGTTGGA TGGTGTGTGTGATTTGTGTTTG
rs563290	ACGTTGGATGGGGAAAATGCTGCAATGAAC	ACGTTGGA TGCTGGGTATTCATCCAGAAG
rs562338	ACGTTGGATGACCCAAGATGTAGAAACAGC	ACGTTGGA TGCCATGGTTTGCATACATCAC
rs581411	ACGTTGGATGACCTGGTGTGCTTAACTGTT	ACGTTGGA TGACAAAGTGAAGAAAGTTGGGC
rs580889	ACGTTGGATGTGGGCTGACTCTTATCTC	ACGTTGGA TGCCCTCTGAAGTGAATAAGCC
rs548145	ACGTTGGATGGAAGGAGGATGGTCAGAAAC	ACGTTGGA TGAGCTGTATCTCCCTTTGTG
rs668948	ACGTTGGATGATTGGAATAGGAAGGGCATG	ACGTTGGA TGCTCTATCGTAATGGGGAAAAG
rs594677	ACGTTGGATGGACTTGGTATTGAACAGGAC	ACGTTGGA TGATAGCAGGCATTTGCACTTTG
rs571468	ACGTTGGATGGTGATGAAATTAAGGCCAGG	ACGTTGGA TGATCTCACTGTTTCTCCAGGG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs4665492	ACGTTGGATGAGTGCCTCACTTCTATTGAC	ACGTTGGATGC CAACAAGCATGTAAGTCAC
rs622236	ACGTTGGATGCGCTTTTCTGTACTGTTGAG	ACGTTGGATGT CCCTTGTCACTACAAAGAC
rs541041	ACGTTGGATGGAGAGGAAAAGGTCACATTC	ACGTTGGATGA TGCAGTAAGAGTAAGTGGC
rs540156	ACGTTGGATGCTTGTCTTTGAAATTCCATAG	ACGTTGGATGC TCTCCTCCATGAATAATTAC
rs1367113	ACGTTGGATGATAATACTGCAGGAGGACAG	ACGTTGGATGA GAACAAATGTCCTTCTCTG
rs1897084	ACGTTGGATGCTTCATCCTCTTAAAAGGTC	ACGTTGGATGC ACAAACCTATGAACTTCC
rs1897083	ACGTTGGATGGTTCAACCTATCATTTTCTTC	ACGTTGGATGT AACTCAATATGGATTAGAC
rs478588	ACGTTGGATGATCTCTTGAACCCAAGAGAT	ACGTTGGATGT GTTTAAGGTTTATGTCTTG
rs664894	ACGTTGGATGCTTGAACCCAAGAGATGGAG	ACGTTGGATGT GGATTCTCTTTCTGCTGCC
rs1594286	ACGTTGGATGCTTGAACCCAAGAGATGGAG	ACGTTGGATGT GAATTCTCTTTCTGCTGCC
rs7422168	ACGTTGGATGCTTGAACCCAAGAGATGGAG	ACGTTGGATGT GAATTCTCTTTCTGCTGCC
rs565202	ACGTTGGATGGCAAAGGCAATTCCATGGAG	ACGTTGGATGC TCGCAGCCTATGTCTTGTT
rs1429974	ACGTTGGATGCTTCATTCTGGTCTGATTTCA	ACGTTGGATGG AAAGAATTCTATCAAGAAG
rs5829769	ACGTTGGATGGTTGGAGCAGATGTTAAGGG	ACGTTGGATGG ATCATGCTTCTGCCTTAAG
rs3056575	ACGTTGGATGGTTGGAGCAGATGTTAAGGG	ACGTTGGATGG ATCATGCTTCTGCCTTAAG
rs6708168	ACGTTGGATGATGGTTACAGTAGCACCCCTG	ACGTTGGATGT TTTTTACGGCAGCCTGAGC
rs6756743	ACGTTGGATGTGGAATCGCAAGTGTAAGTG	ACGTTGGATGT TGCACATGTATCCCAGAAC
rs2195598	ACGTTGGATGATGGGCAAAGACTTCTTGAC	ACGTTGGATGT GCTGTCAGAAGCTCTTTAG
rs7567217	ACGTTGGATGCTCAAACTCTTCTGGCCTC	ACGTTGGATGA ACAGATGCTGGAGAGGATG
rs568938	ACGTTGGATGCTCCTCAGCTAAATATCCAG	ACGTTGGATGA AAGTGGCAAAGTACTTGGC
rs666416	ACGTTGGATGACCCTTTGAACTGAGGTGG	ACGTTGGATGT CAGAAGTCCTTAGGACTGC
rs6761300	ACGTTGGATGCCTACGAAGTAATTTTCTCC	ACGTTGGATGC TATATTGAATGACAAGAGG
rs5829770	ACGTTGGATGCACCTAACTGAGAATACACAG	ACGTTGGATGG CTGTAATTTCTTAGTGGC
rs1429973	ACGTTGGATGAAATATGGCTTGAACCCAGG	ACGTTGGATGT G GAGTGCAGTGGCACGATCT
rs1429972	ACGTTGGATGCTTTCTTTGCTAACCACTGC	ACGTTGGATGC AGAATCTCTCTGAAAGCTG
rs6756284	ACGTTGGATGTGGGATTATAGGCATGAGCC	ACGTTGGATGT TCAGCTTTCAGAGAGATTC
rs749988	ACGTTGGATGTTTTCTATTTGCATCTACTG	ACGTTGGATGG T GACAAAACAAACCAAAGTC
rs749987	ACGTTGGATGGTCTTCAAATATAGTATGGC	ACGTTGGATGA TTTCCAGGGTTTGACTTTG
rs754524	ACGTTGGATGGACTTTCTGGGATTTCTCATC	ACGTTGGATGC TTCCACTCTAAGCCTTAAG
rs754523	ACGTTGGATGGTATTTGCAAAGTAGGTGAC	ACGTTGGATGT CTTGAAAGTGAAAGCCTCC
rs675430	ACGTTGGATGATGAGCATGACACAACAACC	ACGTTGGATGA GGTATCTTCAGAGACACAG
rs600012	ACGTTGGATGACTCCAGCCTGGGAGACAGA	ACGTTGGATGG CCTTGAACCTACACTCAAG
rs614303	ACGTTGGATGCAAACTCACATTCTTTGAC	ACGTTGGATGT TTAATTCCTGCCATGCAC

TABLE 12

dbSNP rs#	Extend Primer	Term Mix
rs1318006	CCCTGACCTGTCACAGGG	ACG
rs1318005	ATGAGAGCCCACCTCCTGT	ACT
rs1318004	TGAGAGCCCACCTCCTGTA	ACG
rs1318003	ACTGGGAGACTCACAGGGA	ACT
rs4327259	GCCACTGGTCCAGCACAG	ACT
rs6756501	GCCACTTCTCCTCCTGCT	ACG
rs6725189	AGAGAGGGCCGACTGCTG	CGT
rs4665709	GTCCCCACCCAAATCTCAC	ACT
rs4665710	GGCGGATTTCTCCTTTGGTG	CGT
rs4371387	GTTCCAGCCATGTAGGTTGT	ACT
rs952274	GGGTGACATGCATTGTGATTT	CGT
rs952275	CCTTCTGCTCAAAAACTTTAC	ACT

dbSNP rs#	Extend Primer	Term Mix
rs1801695	ATTATTTTCTTCGTCGCAATGG	ACG
rs1042034	GAGATCAACACAATCTTCA	ACT
rs1801702	GATAAATCTTTCAACAGTTCC	ACT
rs1042031	TTGGTACGAGTTACTCAA	ACT
rs2678378	AGTCCTAGGAAGGCTTTAATTT	ACG
rs2678379	AGTCAGGAAATGACAGATAGG	ACT
rs1800479	GGTATGGAGATGAAGAAAATCA	ACT
rs1801701	AAAGACCCAGAATGAATC	ACG
rs4362589	GGGCACTTCCAAAATTGATGAT	CGT
rs5742904	CCTGCAGCTTCACTGAAGAC	ACG
rs1799812	GGTGCCCTCTAATTTGTAAGT	ACG
rs2163204	GCTGCGATACCTGCTTCGT	ACT
rs676210	AAGTTCCTGACCTTCACATAC	ACG
rs1042006	CTGATGATCTTTACTTTTCATTTT	ACT
rs1801696	GAACCTTACTGACTTTGCA	ACT
rs693	GGCCAAATTCCGAGAGAC	ACG
rs1041974	GTTGGATTATTGATGATGCTGT	ACT
rs1041968	TTTGACATGCTCAAGAAC	ACT
rs568413	TGGCGTAGAGACCCATCA	ACT
rs2854726	AGCCTGTAGTCAATAACGCC	CGT
rs2854725	AGCTTTGTGTAAGTGGGTAAC	ACT
rs2000998	TATCTGGTTTTGATCACCACAT	CGT
rs2000997	CAGGATTAAACAGAAGTTCCAA	CGT
rs497166	AGTGCTGGGATTACAGGTGT	ACT
rs562956	CGGCTTCTCCTCTTATTTCTG	CGT
rs7589300	AAGGTCCCTGACCTTTGAAC	ACT
rs3791980	GGAAAATTAATATTTTCCCCC	CGT
rs3791981	GAGAATGAAGAAACAATAGCTC	ACG
rs1801700	GACTCGTGGAAGAAGTTGGT	ACT
rs679899	AAGTTGAGATTCTTTCAGA	ACT
rs1041952	CAGAACTCAAGTCTTCAATCCT	ACT
rs6727706	TCCCTAGTGTATGTTTTGTCA	ACT
rs6719207	TGTAACCATGTCAACAGTAGC	CGT
rs1469513	CAAGCCTCTGGCCTTTGAAG	ACT
rs1800478	CATACACGGTATCCTATGGAG	ACT
rs550619	GTGGCCAGGACTCCTCAAT	ACT
rs6752026	GGGAAGCAGGTTTTCTTTAC	ACG
rs579826	TGAGCCACCAGGTCCAGC	ACG
rs597331	CTCTCAGAAAGTTCCCAACAC	ACT
rs1367116	TTAAAGGAACCTAACTAGGGAA	ACT
rs1367117	AGCCATACACCTCTTTCAGG	ACT
rs1800480	GGCACTCAGCCCCGCAG	ACT
rs1800481	TCTCAGACCCTGAGGCGC	ACG
rs934197	CTGCATCCCCCTTCTCTCT	ACG
rs1625764	CATCGAGCGCTGGCTGAAG	ACG
rs1625714	TCCAGCTGGGCAGAGGCA	ACT
rs1560357	CCACTACCGCTGATTCCCT	CGT
rs617314	GTAGCTTGTTACATCTGGGG	ACT
rs547186	GGGAAGACTTGCCAAAGACC	CGT

dbSNP rs#	Extend Primer	Term Mix
rs589566	TCTGAGTTTAGTGCTGTTTAC	ACT
rs588245	AGCCTATCTCGTTTCTGCCT	ACT
rs585967	CTATGAAGTCTAACTGGGCTG	ACT
rs7562777	ATGGTGCCTCGTGCCTGTA	ACT
rs7575840	TCACAGGGAAAGCCAGGAAT	ACT
rs7567653	ACTTCATTAATAACATCGCCGT	ACT
rs6548010	GGTTTTTGGTATACACATATTC	ACT
rs6548011	AAGGATAGAAAAAATATAGTCCC	ACT
rs934198	AGGAGGATGAGTGGGGAGA	ACT
rs634292	CTTGTTTATGGCACAGAAAGATG	ACT
rs1003177	CACCATTTATGCAGGGCTAG	ACT
rs6726115	CTGGTACTTGGTTAATAGTCC	ACT
rs481069	CAGGACCCAGCCCCCA	ACT
rs1367115	TGGATTAGTGAATGGGAGGG	ACT
rs666126	GCAGGATTCATCTCTCCATATA	ACG
rs7566030	TGCCTGCCCCAACCCTCT	ACT
rs7590135	CACCAGGCTGTTTTAGCAGC	ACG
rs6718513	AAGAACAAAAAGAGGATTGGGA	ACT
rs515135	ACAGCCAAAATGGAACCAAAG	ACT
rs1367114	TTGCAGGTCACTTTTTTAAAGTT	ACT
rs563290	AACACAGAAATGCAGATATCTC	ACG
rs562338	CATTGTCTTGACAGATGAATGC	ACT
rs581411	TGATAGAGACAGTTATCAATTC	ACT
rs580889	TCTCCGGCTGGGCCGTC	ACT
rs548145	AGAAACAATGACAGAATACTAAG	ACT
rs668948	GGCATGCTGTCTCCTCTGC	ACT
rs594677	GTATTGAACAGGACTGAGTAAT	ACG
rs571468	GAAGAGAAGGCTGGCGCC	CGT
rs4665492	CCTATAGATAAGACTTTTATTCCA	ACT
rs622236	GTGAATGAATGAATGAATGAACC	CGT
rs541041	CTATTCATGTTTCAGGGCCCA	ACG
rs540156	TACGAGTATATGTATACATTTGC	ACT
rs1367113	GGCTAGATAGGGAAGTGGG	ACT
rs1897084	TCTTAAAAGGTCTTTTGCAAAGA	ACT
rs1897083	TCTATATTTTCTTTTGAAGTTTC	ACT
rs478588	CTGGGCAGCAGAAAGAGAAT	ACG
rs664894	GCCAAGATCATGCCACTGC	CGT
rs1594286	ATGGAGGTTGCAGTGAGCC	ACT
rs7422168	GATGGAGGTTGCAGTGAGC	ACT
rs565202	CAGGAACAATTGGAAGTCTACA	ACG
rs1429974	CTGGTCTGATTCAGTTGCC	ACT
rs5829769	GAGGATATATTCCAGGAGATATA	CGT
rs3056575	CAGAGGATATATTCCAGGAGA	CGT
rs6708168	CCCTGCTTCTCAGTACCAAA	CGT
rs6756743	CGCAAGTGTAAGTGATCAAAG	ACG
rs2195598	ACTAAAACACCAAAAGCAATGG	ACG
rs7567217	ACTCTTCTGGCCTCATCTAC	ACT
rs568938	CCTCACACAAAACACCAGAAC	ACT
rs666416	GCCTGTCCCACTGGGCC	ACG

dbSNP rs#	Extend Primer	Term Mix
rs6761300	GGAATTCTTCAATAATGACAACA	ACT
rs5829770	CTTGATAACATGTACCAAAAAAAAA	CGT
rs1429973	CTTGAACCCAGGAGGCAGA	ACT
rs1429972	GCTAACCCTGCAGCTCCT	ACG
rs6756284	GGCATGAGCCACCGCGC	ACG
rs749988	TCTATTTGCATCTACTGAATTTT	ACG
rs749987	CGAATAAGGAGCTATCTGTGA	ACG
rs754524	TAGAAAACAAGCTATACATTCATA	ACT
rs754523	TGCAAAAGTAGGTGACAATTGC	ACG
rs675430	GTGAAAAATGAACAGATTTGTCC	ACT
rs600012	CTGGGAGACAGAGCGAGATT	ACG
rs614303	CTTTGACAATACATGAGCCCT	ACG

Genetic Analysis

[0253] Allelotyping results from the discovery cohort are shown for cases and controls in Table 13. The allele frequency for the A2 allele is noted in the fifth and sixth columns for osteoarthritis case pools and control pools, respectively, where “AF” is allele frequency. The allele frequency for the A1 allele can be easily calculated by subtracting the A2 allele frequency from 1 (A1 AF = 1-A2 AF). For example, the SNP rs1318006 has the following case and control allele frequencies: case A1 (C) = 0.494; case A2 (T) = 0.506; control A1 (C) = 0.460; and control A2 (T) = 0.540, where the nucleotide is provided in paranthesis. Some SNPs are labeled “untyped” because of failed assays.

TABLE 13

dbSNP rs#	Position in SEQ ID NO: 1	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1318006	238	21188688	C/T	0.506	0.540	0.326
rs1318005	294	21188744	C/T	0.044	0.034	0.643
rs1318004	295	21188745	A/G			
rs1318003	347	21188797	A/C			
rs4327259	1425	21189875	A/C	0.962	0.965	0.865
rs6756501	4891	21193341	C/T	0.195	0.141	0.061
rs6725189	5087	21193537	G/T	0.317	0.250	0.036
rs4665709	7041	21195491	A/G	0.683	0.757	0.014
rs4665710	7121	21195571	A/C	0.206	0.209	0.926
rs4371387	7219	21195669	A/G	0.579	0.688	~0.0001
rs952274	7443	21195893	G/T	0.163	0.123	0.158
rs952275	7485	21195935	G/T	0.234	0.319	0.013
rs1801695	10939	21199389	A/G	0.047	0.071	0.319
rs1042034	11367	21199817	A/G	0.191	0.182	0.743
rs1801702	11571	21200021	C/G			
rs1042031	11839	21200289	A/G	0.686	0.785	0.001
rs2678378	12551	21201001	A/G			
rs2678379	12646	21201096	A/G	0.693	0.714	0.466
rs1800479	13469	21201919	G/C	0.144	0.130	0.687
rs1801701	14913	21203363	A/G	0.090	0.116	0.314
rs4362589	15205	21203655	G/T			
rs5742904	15246	21203696	A/G			
rs1799812	15695	21204145	G/A			
rs2163204	17473	21205923	G/T			
rs676210	17610	21206060	A/G	0.186	0.177	0.758
rs1042006	17828	21206278	A/C			

dbSNP rs#	Position in SEQ ID NO: 1	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1801696	18130	21206580	A/G			
rs693	18281	21206731	C/T	0.494	0.537	0.208
rs1041974	18623	21207073	C/G			
rs1041968	18890	21207340	C/T			
rs568413	21561	21210011	C/T			
rs2854726	23100	21211550	A/T			
rs2854725	23872	21212322	A/C			
rs2000998	24581	21213031	A/T			
rs2000997	24582	21213032	A/T			
rs497166	24983	21213433	C/T			
rs562956	27540	21215990	A/T			
rs7589300	30846	21219296	C/T			
rs3791980	31415	21219865	G/T			
rs3791981	31453	21219903	A/G	0.964	0.968	0.849
rs1801700	31899	21220349	T/C	0.832	0.897	0.008
rs679899	37000	21225450	A/G	0.378	0.474	0.004
rs1041952	38681	21227131	C/G			
rs6727706	39287	21227737	C/T			
rs6719207	42951	21231401	A/T			
rs1469513	45648	21234098	C/T	0.477	0.534	0.079
rs1800478	46222	21234672	C/T			
rs550619	46687	21235137	A/G	0.053	0.062	0.656
rs6752026	47020	21235470	A/G			
rs579826	47593	21236043	C/T	0.069	0.063	0.817
rs597331	48513	21236963	C/T	0.435	0.512	0.014
rs1367116	49723	21238173	A/G			
rs1367117	49986	21238436	A/G	0.431	0.367	0.049
rs1800480	53018	21241468	C/G	0.978	NA	NA
rs1800481	53296	21241746	C/T	0.100	0.082	0.487
rs934197	53547	21241997	A/G	0.338	0.398	0.075
rs1625764	53899	21242349	C/T			
rs1625714	53916	21242366	G/T			
rs1560357	53933	21242383	A/C			
rs617314	54305	21242755	G/T	0.977	0.971	0.741
rs547186	55327	21243777	A/T	0.468	0.490	0.528
rs589566	55895	21244345	C/T	0.386	0.377	0.780
rs588245	56143	21244593	C/T	0.425	0.398	0.397
rs585967	56640	21245090	G/T	0.724	0.781	0.046
rs7562777	58486	21246936	A/G			
rs7575840	59576	21248026	G/T	0.436	0.408	0.422
rs7567653	63048	21251498	A/G	0.918	0.910	0.739
rs6548010	64008	21252458	A/G	0.293	0.345	0.081
rs6548011	64018	21252468	C/T	0.530	0.482	0.135
rs934198	64859	21253309	A/C	0.526	0.484	0.225
rs634292	65995	21254445	G/T	0.456	0.492	0.256
rs1003177	66905	21255355	A/G			
rs6726115	67183	21255633	A/G	0.293	0.342	0.119
rs481069	67942	21256392	C/T	0.138	0.104	0.167
rs1367115	68101	21256551	A/G	0.421	0.408	0.693
rs666126	68521	21256971	A/G	0.500	0.530	0.388
rs7566030	68664	21257114	C/G	0.397	0.416	0.536
rs7590135	68988	21257438	A/G	0.268	0.324	0.082
rs6718513	69178	21257628	C/G			
rs515135	72143	21260593	A/G	0.726	0.747	0.455
rs1367114	74183	21262633	C/G			
rs563290	74312	21262762	C/T	0.667	0.690	0.516
rs562338	74407	21262857	C/T	0.482	0.578	0.006
rs581411	75518	21263968	A/G	0.162	0.157	0.839
rs580889	76153	21264603	A/G	0.127	0.111	0.487
rs548145	77398	21265848	A/G	0.709	0.765	0.049
rs668948	77615	21266065	A/G	0.133	0.127	0.805
rs594677	79092	21267542	C/T			
rs571468	80000	21268450	G/T	0.455	0.502	0.169

dbSNP rs#	Position in SEQ ID NO: 1	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs4665492	80125	21268575	A/C	0.274	0.327	0.088
rs622236	80595	21269045	G/T			
rs541041	81061	21269511	C/T	0.779	0.791	0.694
rs540156	81151	21269601	A/G	0.237	0.277	0.237
rs1367113	81918	21270368	C/T	0.394	0.366	0.370
rs1897084	83072	21271522	C/T			
rs1897083	83137	21271587	C/T	0.279	0.326	0.139
rs478588	83235	21271685	C/T			
rs664894	83263	21271713	A/T	0.319	0.343	0.467
rs1594286	83279	21271729	A/G			
rs7422168	83280	21271730	C/G			
rs565202	83533	21271983	C/T	0.483	0.514	0.373
rs1429974	86856	21275306	G/T	0.583	0.535	0.189
rs5829769	87186	21275636	-/TATA			
rs3056575	87189	21275639	-/ATAT			
rs6708168	87727	21276177	A/T	0.610	0.563	0.163
rs6756743	87978	21276428	C/T	0.051	0.051	0.978
rs2195598	89129	21277579	A/G			
rs7567217	89556	21278006	C/T	0.100	0.087	0.547
rs568938	89702	21278152	A/G	0.177	0.150	0.304
rs666416	90233	21278683	A/G	0.421	0.364	0.093
rs6761300	93060	21281510	A/G	0.271	0.348	0.012
rs5829770	94779	21283229	-/T	0.036	0.037	0.971
rs1429973	95367	21283817	A/G			
rs1429972	95844	21284294	A/G	0.422	0.443	0.533
rs6756284	95942	21284392	A/G	0.155	0.114	0.133
rs749988	96884	21285334	C/T			
rs749987	96938	21285388	A/G			
rs754524	97627	21286077	A/C	0.248	0.306	0.044
rs754523	97777	21286227	C/T	0.567	0.512	0.113
rs675430	97871	21286321	A/C	0.352	0.345	0.812
rs600012	98746	21287196	A/G			
rs614303	99663	21288113	A/G	0.722	0.730	0.805

[0254] Allelotyping results were considered particularly significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The allelotyping p-values were plotted in Figure 1A for the discovery cohort. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figure 1A can be determined by consulting Table 13. For example, the left-most X on the left graph is at position 21188688. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0255] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The generally bottom-most curve is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line

provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0256] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is placed at the 3' end of each gene to show the direction of transcription.

Example 5

IL1RL2 Proximal SNPs

[0257] It has been discovered that rs1024791, which lies within the *IL1RL2* gene, is associated with occurrence of osteoarthritis in subjects. Interleukin-1 receptor-like 2 is a member of the interleukin 1 receptor family. *IL1RL2* inhibits IL-1 activity and contains immunoglobulin domains. This gene and four other interleukin 1 receptor family genes, including interleukin 1 receptor, type I (IL1R1), interleukin 1 receptor, type II (IL1R2), interleukin 1 receptor-like 1 (IL1RL1), and interleukin 18 receptor 1 (*IL18R1*), form a cytokine receptor gene cluster in a region mapped to chromosome 2q12. *IL1RL2* may mediate inflammatory responses that can contribute to the development of OA. *IL1RL2* biological activity can be modulated by addition of an antibody, a recombinant binding partner, a binding agent, or a recombinant *IL1RL2* protein or functional fragment thereof.

[0258] One hundred forty additional allelic variants proximal to rs1024791 were identified and subsequently allelotyped in osteoarthritis case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 14. The chromosome positions provided in column four of Table 14 are based on Genome "Build 34" of NCBI's GenBank.

TABLE 14

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 3	Chromosome Position	Allele Variants
rs3917304	2	225	102409525	G/T
rs2041747	2	509	102409809	C/T
rs3917305	2	860	102410160	C/T
rs3771200	2	874	102410174	C/T
rs3917306	2	939	102410239	A/G
rs3917307	2	1483	102410783	G/T
rs3917308	2	1798	102411098	C/T
rs3917310	2	2189	102411489	A/T
rs3917311	2	2215	102411515	A/G
rs3917312	2	2282	102411582	C/G
rs3917313	2	2340	102411640	C/T
rs3917314	2	2963	102412263	A/C

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 3	Chromosome Position	Allele Variants
rs3917316	2	3369	102412669	-/T
rs3171845	2	3481	102412781	A/G
rs3171846	2	3564	102412864	G/T
rs3917317	2	3653	102412953	-/TC
rs3917318	2	4860	102414160	A/G
rs3917319	2	4941	102414241	A/T
rs3917320	2	4975	102414275	A/C
rs3917321	2	5321	102414621	A/G
rs3917322	2	5346	102414646	A/G
rs3917323	2	5541	102414841	A/G
rs3917324	2	5633	102414933	C/G
rs3917325	2	6007	102415307	G/T
rs3732134	2	6317	102415617	C/G
rs3732133	2	6378	102415678	A/G
rs2110726	2	6382	102415682	C/T
rs3917326	2	6426	102415726	C/T
rs3917327	2	6479	102415779	C/G
rs3917328	2	6641	102415941	C/T
rs3732131	2	6703	102416003	C/T
rs3732130	2	6705	102416005	C/T
rs3917329	2	7963	102417263	G/T
rs3917330	2	8525	102417825	G/T
rs3917331	2	8526	102417826	A/T
rs3917344	2	8598	102417898	C/T
rs3917332	2	8624	102417924	A/T
rs3917333	2	8883	102418183	A/T
rs3917334	2	8980	102418280	G/T
rs1030021	2	13578	102422878	G/T
rs2241132	2	16135	102425435	G/T
rs2241131	2	16141	102425441	G/T
rs3835036	2	16642	102425942	-/TGG
rs1997504	2	16931	102426231	A/G
rs1805232	2	17004	102426304	A/G
rs1971696	2	17009	102426309	C/T
rs1971695	2	17010	102426310	A/G
rs3771199	2	18713	102428013	C/T
rs1922303	2	18853	102428153	C/T
rs3213734	2	20783	102430083	C/T
rs1997503	2	21335	102430635	A/G
rs1558649	2	22180	102431480	C/T
rs1558648	2	22268	102431568	A/C
rs1558647	2	22285	102431585	C/T
rs1558646	2	25378	102434678	C/T
rs1882514	2	25906	102435206	C/G
rs1882513	2	26015	102435315	A/G
rs867770	2	26475	102435775	A/G
rs2310235	2	26798	102436098	A/T
rs870684	2	27042	102436342	A/G
rs3771197	2	27649	102436949	A/G
rs3771196	2	27827	102437127	A/T
rs3821207	2	27873	102437173	A/G
rs3771195	2	28122	102437422	A/G

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 3	Chromosome Position	Allele Variants
rs3771194	2	28202	102437502	A/G
rs3771193	2	28232	102437532	A/C
rs3771192	2	28240	102437540	G/T
rs3755290	2	29546	102438846	G/T
rs3821206	2	29748	102439048	A/G
rs2302623	2	30054	102439354	A/T
rs3755289	2	30646	102439946	G/T
rs1922302	2	31149	102440449	A/C
rs2110725	2	36912	102446212	A/C
rs1465326	2	36936	102446236	C/G
rs2871458	2	37184	102446484	C/T
rs2080310	2	39064	102448364	C/T
rs1922289	2	39343	102448643	G/T
rs1922290	2	40868	102450168	C/G
rs1922291	2	40917	102450217	A/G
rs1922292	2	41113	102450413	A/C
rs3815517	2	47343	102456643	A/T
rs2241130	2	47806	102457106	A/G
rs1922295	2	47911	102457211	A/G
rs1922294	2	48009	102457309	C/T
rs2302622	2	48621	102457921	C/G
rs2310240	2	49245	102458545	C/G
rs1024792	2	49247	102458547	C/G
rs3836112	2	49299	102458599	-/CTCT
rs3074969	2	49302	102458602	-/AGAG
rs917994	2	49514	102458814	C/T
rs2041753	2	49626	102458926	G/T
rs2041752	2	49791	102459091	A/G
rs1024791	2	50010	102459310	A/G
rs1024790	2	50294	102459594	A/G
rs995515	2	51482	102460782	A/G/T
rs995514	2	51556	102460856	A/G
rs1922293	2	51855	102461155	A/G
rs3755287	2	51956	102461256	C/T
rs3729564	2	52155	102461455	A/G
rs3771188	2	52448	102461748	A/G
rs3771187	2	52458	102461758	C/T
rs3771186	2	52511	102461811	C/T
rs3771185	2	52607	102461907	A/G
rs2310241	2	54049	102463349	A/C
rs2302621	2	54224	102463524	A/C
rs2302620	2	54567	102463867	A/G
rs3771184	2	55052	102464352	C/T
rs3834161	2	55857	102465157	-/C
rs3755286	2	55941	102465241	C/G
rs3755285	2	56120	102465420	A/G
rs1997502	2	56349	102465649	C/T
rs3771182	2	56727	102466027	A/G
rs3836111	2	57232	102466532	-/CT
rs3771181	2	58806	102468106	C/T
rs955754	2	61181	102470481	C/T
rs2302612	2	63808	102473108	A/G

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 3	Chromosome Position	Allele Variants
rs3755284	2	64526	102473826	A/T
rs3821205	2	64865	102474165	A/G
rs3815511	2	64928	102474228	C/T
rs2287041	2	64966	102474266	A/C
rs2287040	2	65080	102474380	A/G
rs2287039	2	65690	102474990	C/T
rs3755283	2	66228	102475528	A/G
rs3755282	2	66982	102476282	A/G
rs1812326	2	72511	102481811	A/G
rs1558626	2	74170	102483470	A/T
rs1558625	2	74264	102483564	C/T
rs1558624	2	74333	102483633	C/T
rs1558623	2	74502	102483802	A/T
rs1035131	2	74741	102484041	A/C
rs2110661	2	75321	102484621	C/T
rs1420093	2	82558	102491858	A/G
rs3074971	2	85366	102494666	-/TTG
rs1345302	2	85469	102494769	C/T
rs1420092	2	86485	102495785	G/T
rs1345301	2	87687	102496987	C/T
rs2310242	2	89463	102498763	G/T
rs2310243	2	89660	102498960	A/G
rs1882510	2	95718	102505018	C/T
rs1882511	2	95821	102505121	A/G

Assay for Verifying and Allelotyping SNPs

[0259] The methods used to verify and allelotype the 140 proximal SNPs of Table 14 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 15 and Table 16, respectively.

TABLE 15

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs3917304	ACGTTGGATGCAGAGAAGATAAGGAATGAG	ACGTTGGATGAAGGAAAATTACCCTAAACC
rs2041747	ACGTTGGATGGGGAAGACTATTACAGGTATG	ACGTTGGATGTAGGAGCAACTAACACTTGC
rs3917305	ACGTTGGATGGTTGTGAAGGAGAGGTCATG	ACGTTGGATGCGAAAGCCTCTACTGGTTTC
rs3771200	ACGTTGGATGCTGGTTTCCTACTGCTCATC	ACGTTGGATGAGTGCTTTGCAGGTGTTGTG
rs3917306	ACGTTGGATGCACCTGCAAAGCACTTTGTC	ACGTTGGATGTGCATTGTGTTCTCCATGGG
rs3917307	ACGTTGGATGCTGTAGTAAGATTCCATGAC	ACGTTGGATGACCCAAGTAATGAGGAAGTG
rs3917308	ACGTTGGATGCAGTGACTTCTGATGTCCTC	ACGTTGGATGAAGTTAGGTCTGGTACATTG
rs3917310	ACGTTGGATGGAGAAGAAGTAATGGAAGG	ACGTTGGATGGGGAAGAAGTAATGGAAGG
rs3917311	ACGTTGGATGCCATAGATTCAATTTGGGGAAG	ACGTTGGATGGAGAAGAAGTAATGGAAGG
rs3917312	ACGTTGGATGCCATACAAACACTGACTCTC	ACGTTGGATGGAAGATATCAGTTCTTCCCC
rs3917313	ACGTTGGATGCACCATGACTATACTTGGTC	ACGTTGGATGTCAGTGTTTGTATGGGTGTG
rs3917314	ACGTTGGATGGGCCTGCATTTCAGACAATAT	ACGTTGGATGGAACTTCATAGAATGCACC
rs3917316	ACGTTGGATGAGTATTCTTGATATGCCAC	ACGTTGGATGGTTAGGAGATGTAGAAGATG
rs3171845	ACGTTGGATGGAAGTCATTAGGCTGAATATC	ACGTTGGATGACAGATGCTCTAAATACCTG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs3171846	ACGTTGGATGTGTCTCTATTTCATCACAGAGC	ACGTTGGATGCTGCCTCAACATTCATATTGG
rs3917317	ACGTTGGATGTCTCAGCCCTGAATTCTATC	ACGTTGGATGGACTAGATCTTCATGCATCAG
rs3917318	ACGTTGGATGAAAAGCCTTGTGTGGCTTTG	ACGTTGGATGGTCTGAAAAACAGGAAGCAC
rs3917319	ACGTTGGATGGTGCTTCCTGTTTTTCAGAC	ACGTTGGATGAAGCCTGATGTTTCTCTGAC
rs3917320	ACGTTGGATGCGTAAAGAAAAGCAGAAGAC	ACGTTGGATGTTGCTCTTCAGATGAACCAC
rs3917321	ACGTTGGATGAGGAGAACTGCAAAGAGAG	ACGTTGGATGACAGGAGGCACCTAAAGAAC
rs3917322	ACGTTGGATGAGTCAGCATGAGGCATAACC	ACGTTGGATGAGCATGGAGAAAGTTGCCAAG
rs3917323	ACGTTGGATGACTTCAGAGTAGAGGGCTTG	ACGTTGGATGAAGTGCTGGGATTATAGGCG
rs3917324	ACGTTGGATGATCACAGAGGTCAGGAGTT	ACGTTGGATGCCACCATGCCTAGCTCATTT
rs3917325	ACGTTGGATGTAGTTAAGTCATCCACAGCC	ACGTTGGATGTGTCACTCTCACTTTGCCTG
rs3732134	ACGTTGGATGTTAATGCTTTCTCCCTGGC	ACGTTGGATGTAGGGAGCTGTTCTCCAAA
rs3732133	ACGTTGGATGAAGGATGGTTCATGTGTGGG	ACGTTGGATGTTACGTCTTTGGAGGAACAG
rs2110726	ACGTTGGATGAAGGATGGTTCATGTGTGGG	ACGTTGGATGTACGTCTTTGGAGGAACAGC
rs3917326	ACGTTGGATGTGCACAGCCACACATGAAC	ACGTTGGATGTTCACTCTCTGAACAGGTGG
rs3917327	ACGTTGGATGAAAAGCATGGGCTTCAGCTCC	ACGTTGGATGATGCCGCTCTTCTGTCTATCC
rs3917328	ACGTTGGATGTAGGCAAAGGAGGAGGAAGG	ACGTTGGATGTGTGTGAATTCAGGTTGG
rs3732131	ACGTTGGATGAGGCCCTTCTCGCATTTTCTC	ACGTTGGATGTCCAGAGACTGTGGAATTG
rs3732130	ACGTTGGATGTCCAGAGACTGTGGAATTG	ACGTTGGATGAGGCCCTTCTCGCATTTTCTC
rs3917329	ACGTTGGATGAAGTCAAAGGAAGTTCACGG	ACGTTGGATGGTGCAAAGTTATTCCTCATC
rs3917330	ACGTTGGATGTAAGCCAATAGCCTCTGACC	ACGTTGGATGAACAAGGTGAGGAGACCTTC
rs3917331	ACGTTGGATGAACAAGGTGAGGAGACCTTC	ACGTTGGATGTAAGCCAATAGCCTCTGACC
rs3917344	ACGTTGGATGAGAGTTCTTCTGTTGTGGG	ACGTTGGATGTAGAAGAAGGGAGTTAGGGC
rs3917332	ACGTTGGATGATTGGCTTAACAGTGAGCCC	ACGTTGGATGAGAAGCAAATGAGCAGAGGG
rs3917333	ACGTTGGATGTAAAGAGGAGGCACTGACTG	ACGTTGGATGGCTGTCCAAATGCATGCTC
rs3917334	ACGTTGGATGGACTCAGACTCTAAGCCAAC	ACGTTGGATGAGTCAGTGCCCTCCTTCTTAC
rs1030021	ACGTTGGATGCAATTGCTTCATGTTCTTACC	ACGTTGGATGAAAAGTGGGCATAACCTCTC
rs2241132	ACGTTGGATGAGGAGGATGGGCGAGGAGTA	ACGTTGGATGTCTGGACACCAGCCTGCTTC
rs2241131	ACGTTGGATGAGGAGGATGGGCGAGGAGTA	ACGTTGGATGCTGTCAAGGTGGCAGAAGCAG
rs3835036	ACGTTGGATGTTCCGCGGAAGAGGAAACAG	ACGTTGGATGTCACCTCCAAGCTCAAAGGC
rs1997504	ACGTTGGATGCCGTGAATCCCAGTACTTTG	ACGTTGGATGTGTTAGCCAGGATGGTCTAG
rs1805232	ACGTTGGATGTTGAGTAGCTGGGACTACAG	ACGTTGGATGTAACACGGTGAAACCCCGTC
rs1971696	ACGTTGGATGTAGACCATCCTGGCTAACAC	ACGTTGGATGTTGAGTAGCTGGGACTACAG
rs1971695	ACGTTGGATGTTGAGTAGCTGGGACTACAG	ACGTTGGATGTAGACCATCCTGGCTAACAC
rs3771199	ACGTTGGATGTGAATAACACAGGCCTGCTG	ACGTTGGATGGCTTGACCTGAATAGACAGC
rs1922303	ACGTTGGATGGTGGGGCCTGAATAAAACAC	ACGTTGGATGTAAGGTCATGCAAGCCAGTG
rs3213734	ACGTTGGATGAACCCACTGTTTTTATAGG	ACGTTGGATGTGACTGCTAGCTAATAATC
rs1997503	ACGTTGGATGAAAACCTCATGACCCAGAGGG	ACGTTGGATGGCACAGGCTAGTCATTTGAG
rs1558649	ACGTTGGATGTGCATGGTGGTTCATGCCTG	ACGTTGGATGAATCTTGCTATGATGCCAG
rs1558648	ACGTTGGATGAGATTTCTACAACCTTGTG	ACGTTGGATGAGGTACATTTTATACCCACC
rs1558647	ACGTTGGATGGAAAAATGTGGTCAATCTCAC	ACGTTGGATGCAACCTTGTGTTGAACCTTG
rs1558646	ACGTTGGATGGGCCTTGTTAGAGTTTAGG	ACGTTGGATGGCTTTAGGTTGGCATAAATGG
rs1882514	ACGTTGGATGTTCTTTCTGTCCATCCTG	ACGTTGGATGCAGAGTTGAGGTACTGGAAG
rs1882513	ACGTTGGATGAAAGTAGAGAGGTCAGGTGG	ACGTTGGATGGGGCATTACACTTTTCCACC
rs867770	ACGTTGGATGGCAGGTGGTGTATTTTCAGAG	ACGTTGGATGACACTGCAGAAGTAGCTTGC
rs2310235	ACGTTGGATGGAGCTGGAATAGGGAATCAG	ACGTTGGATGGCCATTATCCAGAACCTCTG
rs870684	ACGTTGGATGCCCAAATTACTCCTCAGCAC	ACGTTGGATGAGAGCGCGAAGTAACCTTCAG
rs3771197	ACGTTGGATGTAAGCAGTTCAGTCCACAG	ACGTTGGATGCCTTTGCTTACCTAAGACTG
rs3771196	ACGTTGGATGCCTTTAACTACACAGCAAC	ACGTTGGATGAGAAGCTTTCTGAGCAAGAG
rs3821207	ACGTTGGATGAAAACCATGAAGAGGAGACG	ACGTTGGATGGCAACTAAAGGATCTTTCTC
rs3771195	ACGTTGGATGGTGGACGCTATTGTTCTTAAC	ACGTTGGATGTAACTCTCAATGAGCTTGG
rs3771194	ACGTTGGATGATCTTAAAGTTCAGCCTTGC	ACGTTGGATGATAATGTTCCAGTGGATCAG
rs3771193	ACGTTGGATGGTTCAGTGGATCAGAATAG	ACGTTGGATGTTAAAGTTCAGCCTTGCAGC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs3771192	ACGTTGGATGGGGTTTCATTCTTTCTTTCAAG	ACGTTGGATGATAGCAAAGCGACAGAATGG
rs3755290	ACGTTGGATGCCCAATTACACTTTCTGCAC	ACGTTGGATGTGATCACTGTTTCAGACCTTC
rs3821206	ACGTTGGATGAGAGTGGCCTACATGAGTTG	ACGTTGGATGCCTCCTGCAAAAACTGACC
rs2302623	ACGTTGGATGGAATACTTAGAAACCTGTGTG	ACGTTGGATGATCTGTTGTCTTCCAGTTAG
rs3755289	ACGTTGGATGTCCAGAACTCTGAGCTCTGC	ACGTTGGATGCCTCAGCCTTCATTGTCTGTG
rs1922302	ACGTTGGATGGAGATCTTTCACCTTCTTTGG	ACGTTGGATGGCCACACATAAAACCATATC
rs2110725	ACGTTGGATGATTCTCTCCCAAGCTATAC	ACGTTGGATGCAATAACCAGGTTTGTGACC
rs1465326	ACGTTGGATGTGTGTTTGAAAAACCAATG	ACGTTGGATGTTTACAGAGTTCCAGGAGGG
rs2871458	ACGTTGGATGAGATCCCCATAGGGATCCAC	ACGTTGGATGCACACTTCAGAGTACTAGGG
rs2080310	ACGTTGGATGGAATGATCCATTCCAGGGTG	ACGTTGGATGGACATCATGTTACCTGTGCC
rs1922289	ACGTTGGATGTGAGTTTGGTCAATTGCTACG	ACGTTGGATGATACAGGCCATGACCTACTC
rs1922290	ACGTTGGATGACACCCAGTTTCCAGCTTTG	ACGTTGGATGCTTCGGCTCTCTGGTGTGTTT
rs1922291	ACGTTGGATGGACTTCTCTGCTACCACAAC	ACGTTGGATGCTCATGGGGAGAGGAATCAA
rs1922292	ACGTTGGATGATATTACCTCACAATGCAAG	ACGTTGGATGATGCTTATTGATCCTTTTCC
rs3815517	ACGTTGGATGACAATGGTTGTCCTGGAAGG	ACGTTGGATGAATAGCCCCCTAGGCCAAATG
rs2241130	ACGTTGGATGGAGAAATGGATCTTACTGCTC	ACGTTGGATGCAATCCACCTATCACATAG
rs1922295	ACGTTGGATGGTTATATCATGAGCCATCGG	ACGTTGGATGGTGTCAATTCAGTGTGTTGC
rs1922294	ACGTTGGATGCGGGCATACAAAGCAAACAC	ACGTTGGATGACTGTCTTCCCTAAGAGTCC
rs2302622	ACGTTGGATGTACTCCAGTGGGTTACACAC	ACGTTGGATGGCATTAGAGTCACTGCTCC
rs2310240	ACGTTGGATGAAATTCAAGTCTCTCTCTT	ACGTTGGATGGTGGTTTACCAAGACAGTTG
rs1024792	ACGTTGGATGGCTGTGTGGTTTACCAAGAC	ACGTTGGATGCCACACACGTGCGTGTCAAA
rs3836112	ACGTTGGATGACGCACGTGTGTGGCTAGCTA	ACGTTGGATGGATGTATGCAAGCATAGG
rs3074969	ACGTTGGATGACGTGTGTGGCTAGCTACAT	ACGTTGGATGGGCTTTAGCTTGATGTATGC
rs917994	ACGTTGGATGCCTCCCTTAGAATTGCAGTG	ACGTTGGATGAAGCAGAGAATGTGCACACC
rs2041753	ACGTTGGATGTCCACATGTTGCAACCCAAG	ACGTTGGATGTAAGTGTGAGTGAGCACAGC
rs2041752	ACGTTGGATGGAACCTCTTAGAGGTACCAG	ACGTTGGATGTCTTCTCCATCACTTTCCC
rs1024791	ACGTTGGATGGTGTAAGGGACTGCAGATAC	ACGTTGGATGAAACAGAACCAGGAGGTTGG
rs1024790	ACGTTGGATGAGAAAATTCAGCTGATTCT	ACGTTGGATGGACTCCTGCCCTACACTTTAA
rs995515	ACGTTGGATGTGGGATGGAATCGCTATTG	ACGTTGGATGTGTCCCAACCTAGAAGTTTG
rs995514	ACGTTGGATGGCTTGGACTTGGCCTCAGAA	ACGTTGGATGCCAATAGCGATTTCCATCCC
rs1922293	ACGTTGGATGGGACAGAGCTAAGGTTATAG	ACGTTGGATGGATTCAAATCTGGAGGTGTC
rs3755287	ACGTTGGATGAAATTGGGTGTGCTCTTCCG	ACGTTGGATGGACTACTACCAGCCTTCAAC
rs3729564	ACGTTGGATGCCTGAGTCCCTCTGAATGTA	ACGTTGGATGTGCCTTCGAGAGTACTGATG
rs3771188	ACGTTGGATGAATCCAATCCTGGGCACTTG	ACGTTGGATGAGAGTAGAGGATGAGGAAGC
rs3771187	ACGTTGGATGAGAGTAGAGGATGAGGAAGC	ACGTTGGATGAATCCAATCCTGGGCACTTG
rs3771186	ACGTTGGATGAAGTGCCAGGATTGGATTG	ACGTTGGATGGAGTAAGTCCAATGCAGCC
rs3771185	ACGTTGGATGATCTTGAGGCCCAAGATTTT	ACGTTGGATGGGCACCAAATGTGTTCTTAG
rs2310241	ACGTTGGATGACCTTCTCCAGCTGGTTCTG	ACGTTGGATGTGGGAGTCCAGCTGTTCAAC
rs2302621	ACGTTGGATGCGTCTACCACCGGAACTAG	ACGTTGGATGGGAAACAAGTCAGCTCCTGG
rs2302620	ACGTTGGATGGTCTCTGTAGAATGGAAGGC	ACGTTGGATGTGGCTGTGTCTGTTGTGTAC
rs3771184	ACGTTGGATGTCTCTCTAGGCCCTGTACTT	ACGTTGGATGACTTGGTTTGATCTCTCTCC
rs3834161	ACGTTGGATGAGGGAAACTGGTTGTCTGAG	ACGTTGGATGCAAAGCAAGCACTTGATGCC
rs3755286	ACGTTGGATGGCATCAAGTGCTTGCTTTGC	ACGTTGGATGCAAGTTAGTGAATAGCCACG
rs3755285	ACGTTGGATGTGCAGATGCCAGAGCCAAAA	ACGTTGGATGACCTGAAGTGCTGCTAGTAC
rs1997502	ACGTTGGATGCGTATTCTTCTGGAAGCTC	ACGTTGGATGTCACTGACAGAGTCAGTGAG
rs3771182	ACGTTGGATGGCCAACACACAGAGATATTAC	ACGTTGGATGGTATGTGTGCATTTTGTGATG
rs3836111	ACGTTGGATGTCTACCCCGACTTGTTTTCC	ACGTTGGATGGGCTAAAACGAAGACAAGCC
rs3771181	ACGTTGGATGTTCTTCTCCAAAAGTTTCC	ACGTTGGATGGCCAGAGGATTTTTTTTCCG
rs955754	ACGTTGGATGGTGATGTGGCCAGAAATGAG	ACGTTGGATGTATCCTCCTGCTTCAGCTTG
rs2302612	ACGTTGGATGTGACAAACCTCGTGTCTCTCC	ACGTTGGATGAAGGTGTGCGCCGTTTCTCTC
rs3755284	ACGTTGGATGGCTGCTCAGAAATCTGGTTG	ACGTTGGATGACCCTTCCATGTTTGAGAGG
rs3821205	ACGTTGGATGATGCCATCCTAAGACCACAG	ACGTTGGATGCTTAGTAAGCAGTCAGTGGG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs3815511	ACGTTGGATGTACCACCCATCGCCTGTGAA	ACGTTGGATGGTGGTCTTAGGATGGCATGG
rs2287041	ACGTTGGATGTGAAAGTCCATCCCACACTG	ACGTTGGATGTGTGGTCTTAGGATGGCATG
rs2287040	ACGTTGGATGATAAAGAGTGGACCAATGTC	ACGTTGGATGTTATGTTCCAAGGTGACCTC
rs2287039	ACGTTGGATGTTTACAGGCACACCCCTTCAG	ACGTTGGATGAGCCACAGTGTGGGGAGAGT
rs3755283	ACGTTGGATGTTCTTGCTGCATTGCATCCC	ACGTTGGATGGGAGAGAGAAATCGAGATGC
rs3755282	ACGTTGGATGGAGGACCAAGCAAGATGAAG	ACGTTGGATGATATTTTGGCAGGCCAGCTC
rs1812326	ACGTTGGATGTTCAAGTGATTCTACTGCCG	ACGTTGGATGAACCCCCGTCTCTACTAAAC
rs1558626	ACGTTGGATGACCTCCAAGCATGATCTCAG	ACGTTGGATGTGGTTTTCCCTTGGTACTCG
rs1558625	ACGTTGGATGTCAGCAAAGCAGGACCGACC	ACGTTGGATGTGAGATCATGCTTGGAGGTC
rs1558624	ACGTTGGATGGGAAAGAACGGCCTGTCTTC	ACGTTGGATGATCCACAGGGTTCGTGTTGT
rs1558623	ACGTTGGATGAAGTCCCAAACCCAAGTGAG	ACGTTGGATGTTAGGAAGCGAAGGAAAAAC
rs1035131	ACGTTGGATGACTCTTCTACCTTGATGGC	ACGTTGGATGTAGGCTTCAGGATTGGATGG
rs2110661	ACGTTGGATGTCCCTCCAAACCCACCTTT	ACGTTGGATGTGGATGGTGACACCTTCATG
rs1420093	ACGTTGGATGAAGAAATTTAAAGCCAGAG	ACGTTGGATGTATCTCAATAGAGGCTCTAC
rs3074971	ACGTTGGATGAAACAAACTGAACCGCTAGG	ACGTTGGATGCAGCGTTCTTCTGGGTATTT
rs1345302	ACGTTGGATGGGTAATCAGAAAACAGAGTC	ACGTTGGATGTGCCAGTAGAAGTACAGTAG
rs1420092	ACGTTGGATGGTGCTCAGAGATGGTTAAAC	ACGTTGGATGACTGCACCCTAGTTGATTTG
rs1345301	ACGTTGGATGGCTCAAGTCTGGAGAAATGA	ACGTTGGATGCATGGTTGGATTTTGTGTTG
rs2310242	ACGTTGGATGCCACCACTCAAACCTTTGTC	ACGTTGGATGGACAGCAAGAGTGAAACTCC
rs2310243	ACGTTGGATGTGTAGCTAAGCACTATAGCG	ACGTTGGATGGCTCCTTCTAGATATGCATG
rs1882510	ACGTTGGATGCTCGCTAGTCACTGGAGCTG	ACGTTGGATGAAGTCCAGGTGGACCTGGT
rs1882511	ACGTTGGATGAAGGAAGTGCAGGGCCATG	ACGTTGGATGAATGGTGCAACTGCCTGGG

TABLE 16

dbSNP rs#	Extend Primer	Term Mix
rs3917304	GGTACTAATGGTGGTTTTCTCTG	ACT
rs2041747	ATGCTAAGAGTTATTCACATTTTG	ACT
rs3917305	GGAGATCCTTGTCCCATAGAT	ACT
rs3771200	TACTGCTCATCTATGGGACAA	ACT
rs3917306	GCACTTTGTCATCTGCCCA	ACT
rs3917307	AAGTTTGAAATGCCATTTCTCT	ACT
rs3917308	TAGTCTTACCCTATGCATCATCA	ACT
rs3917310	ATGGAAAGGATATACAATGTTTCA	CGT
rs3917311	ATTCATTGGGGAAGAACTGATA	ACG
rs3917312	TACAAACACTGACTCTCACTTGTA	ACT
rs3917313	CTTGGTCCTTTACAGTTCCCT	ACT
rs3917314	GGATACTAATGTACAAAGCAATGA	ACT
rs3917316	ATTTTAGAAACCCTCTTAGTAAAA	CGT
rs3171845	TGAATATCATTGTTTTCTAA	ACT
rs3171846	ATCACAGAGCAAGGCCTA	CGT
rs3917317	AGTTTAAACAAAGGAGAGAGAGA	ACT
rs3917318	GTGTGGCTTTGGTTCAGGAG	ACT
rs3917319	GTTGAGGTCATTAATGAAAACGT	CGT
rs3917320	GAAGACTGATTATCATTTTAGTC	CGT
rs3917321	ACGTGCCTCTCGGGTAGC	ACT
rs3917322	CCATAAGACAGGAGGCACC	ACG
rs3917323	GGGAAGATCTTTTAAAAAGGCA	ACT

dbSNP rs#	Extend Primer	Term Mix
rs3917324	TCAGGAGTTCCGAGACCAGC	ACT
rs3917325	CCTGTAGAGTCACTGACCC	ACT
rs3732134	TTCTCCCTGGCATGACCAT	ACT
rs3732133	CAAGGGACATTGCAGACGGA	ACT
rs2110726	TGCAAGGGACATTGCAGA	ACG
rs3917326	CCCACACATGAACCATCCTTCC	ACG
rs3917327	GCTTCAGCTCC TGAACAGGTG	ACT
rs3917328	GGAGGAAGGGTGCAGGCAA	ACT
rs3732131	TCTCGCATTTTCTCTAGCTGATC	ACT
rs3732130	GGATGTTCTGAA TTTTGGTAAAT	ACG
rs3917329	CTTCTTCCTCCAGAATTCAAC	CGT
rs3917330	TCCCCACAACAGGAAGAACT	CGT
rs3917331	TGAGGAGACCTTCTGCAGAG	CGT
rs3917344	GAGTGGAGGTCAGAGGCTAT	ACG
rs3917332	ACAGTGAGCCCTAACTCCC	CGT
rs3917333	GGGTGTCATCTCTGACCATC	CGT
rs3917334	TCAGACTCTAAGCCAACCTGCCA	CGT
rs1030021	CTTTTAAATTTTGCCAGTTTGC	ACT
rs2241132	CGGTGGGGACCGCGTGG	ACT
rs2241131	CGGCGGCGGTGGGGACC	ACT
rs3835036	GCGGAAGAGGAAACAGAGAACCA	ACT
rs1997504	GCGGGCGGATCACGAGG	ACG
rs1805232	CGCCCGCCACCGCGCCC	ACT
rs1971696	ACATTAAAAAAATTAGCCGGGC	ACT
rs1971695	TACAGGCGC CCGCCACC	ACT
rs3771199	TGACTGTGGTCAGCTGGAAA	ACT
rs1922303	GGGGCCTGAATAAAACACATCTGT	ACT
rs3213734	TTTAAGGCAGAA TTGGTAAAGAAA	ACT
rs1997503	AGAGGGGTGTGCTGGCAGGC	ACT
rs1558649	GGTGGTTCATGCCTGTAATCC	ACG
rs1558648	TGTTGAACTTTGTATTATAAGCC	ACT
rs1558647	GGTACATTTTATACCCACCAAA	ACG
rs1558646	CTTGGTTAGAGTTTAGGGCACAT	ACT
rs1882514	GGATTCACGTGTCCATCACTT	ACT
rs1882513	GTGGGCTAATTCCAGTTAAGA	ACG
rs867770	AGAAGTAGCTTGCCCTGAGAGC	ACG
rs2310235	GGGAATCAGTCAGAAAGTAATA	CGT
rs870684	CACAGTGTTTTTGGGTCCC	ACG
rs3771197	GTTCCAGTCCACAGAATTTAGT	ACT
rs3771196	CTACACAGCAACTAAAGGATC	CGT
rs3821207	AAGAGGAGACGAGCATCAGA	ACT
rs3771195	TTAAATCTTGTTAGTGAGACATTA	ACG
rs3771194	TGTCGCTTTGCTATAACTTAGACT	ACT
rs3771193	GTTATAGCAAAGCGACAGAATG	ACT
rs3771192	CATCTTAAAGTTCAGCCTTGCA	ACT
rs3755290	TGCACTTATCAAGCATTGGAC	ACT
rs3821206	GGAAGGAAGACTTCATGGAG	ACT
rs2302623	GAAACCTGTGTGATCCCTAG	CGT
rs3755289	TCAGCTGGAAGGCCCGCA	ACT

dbSNP rs#	Extend Primer	Term Mix
rs1922302	TTAATTCCTAGGTATTTAATTTCG	ACT
rs2110725	CATTTTACAGAGTTCCAGGAGGG	ACT
rs1465326	GGCTCTGTTTCTGACAATAACCAG	ACT
rs2871458	GGATCCACACCACCCAGAA	ACT
rs2080310	GGTGGATCAGAAGTGCAAGGT	ACT
rs1922289	CATTGCTACGTTGAGTATGAG	ACT
rs1922290	CCCAGTTTCCAGCTTTGGATATAC	ACT
rs1922291	TCTGCTACCACAACCTTTTCCA	ACG
rs1922292	ACCTCACAATGCAAGATATATTA	CGT
rs3815517	GCCACTTGCCCCCTTGTGG	CGT
rs2241130	GATCTTACTGCTCTCAGG GAT	ACT
rs1922295	GCCTTCAAAGCTTAATGCC	ACG
rs1922294	GTTCTTTGCTATACTAAACAAGC	ACT
rs2302622	CACACTGTTGAGAGTGTTCAAAAC	ACT
rs2310240	TGCAAACACACACACACACACA	ACT
rs1024792	CGTGTCAAACACACACACACACA	ACT
rs3836112	TGGCTAGCTACATGCAAGAG	ACT
rs3074969	TGGCTAGCTACATGCAAGAG	ACT
rs917994	CAGTGAATAGGGATCTGTGC	ACT
rs2041753	CCCATGTGCTCAGGGTGAG	ACT
rs2041752	CTTAGAGGTACCAGAGAGAGA	ACT
rs1024791	CTGGCTGATGTCAGAAAGCA	ACG
rs1024790	CACAGAGAGGTTGAGTGACA	ACT
rs995515	CTATTGGTCAGCTTCAGTCTAT	ACT
rs995514	ACTTGGCCTCAGAATCC TTC	ACT
rs1922293	GCTTCTCCATTTGACTTCCTTA	ACG
rs3755287	GGTGTGCTCTTCCGTGAATTCGC	ACT
rs3729564	TTCCAATTTCAATTCTCTTTTAGCT	ACG
rs3771188	TGTGAGAACCCCTCACTTCA	ACT
rs3771187	TCTGTCTTATGATTGAAGTGAG	ACT
rs3771186	CGGTGTGTGGTGCAAGTGC	ACT
rs3771185	AGGCCCAAGATTTCTCATTACT	ACT
rs2310241	CAGCTGGTTCTGCTGCC	ACT
rs2302621	GGGCTCTGCAGACTTTTACTC	ACT
rs2302620	CTGTAGAATGGAAGGCAC TCG	ACT
rs3771184	CCCTGTACTTGGTGCTGAAG	ACT
rs3834161	GTTGTCTGAGAACGTTTTATGGG	ACT
rs3755286	AGTACGTTGTTGCCACAT	ACT
rs3755285	ACCCCTCCCATGCC	ACT
rs1997502	TCCTGGAAGCTCAGGCC	ACT
rs3771182	GTTCTCGTAGACAGAGCTGT	ACT
rs3836111	CCTTGGTTTCCCTTTGATCACT	CGT
rs3771181	TCAGAAACATAAGAACTTATGAA	ACT
rs955754	GCCAGAAATGAGAATTAAAGGCAG	ACT
rs2302612	GTAGCAAGGTGTGTGCTGC	ACT
rs3755284	TGTCTAAAAGAGAGAGAAAGG	CGT
rs3821205	CCTCTGGCTCCCTCTCTC	ACT
rs3815511	GGCACAGCACCTCCTAACC	ACG
rs2287041	CATCCCACACTGGGTACCA	CGT

dbSNP rs#	Extend Primer	Term Mix
rs2287040	TGGACCAATGTCAAGTCGAG	ACT
rs2287039	CAGAGAGGACACGTCCCC	ACT
rs3755283	CCTATTATTTTCATTAGGAATTAGT	ACT
rs3755282	CATGTGAAAAGTGCTTGGCAAAC	ACG
rs1812326	AGGTGCATGCCACCACACT	ACG
rs1558626	TTCAGGCTAGTTTCACCCGA	CGT
rs1558625	GCAGGACCGACCCTCCCT	ACG
rs1558624	GGCCTGTCTTCAGGGCTC	ACT
rs1558623	AAGTGAGGGCTCCAGCGAT	CGT
rs1035131	GATGGCACATCTCTAGAAAAG	CGT
rs2110661	GTCTCTCCTCAGATATGAGCC	ACG
rs1420093	TTTAAAGCCCAGAGATTTTAAAAA	ACT
rs3074971	CTAGGAAAAAAGAAAGGCAACA	CGT
rs1345302	GAAAACAGAGTCTTTACCAATC	ACT
rs1420092	AGAGATGGTTAAACAGGCACA	ACT
rs1345301	CACAAGTTTACACCTTTTCTTTA	ACT
rs2310242	CTCTATAACCTTACAAATGTTATT	CGT
rs2310243	TGCAGTTTGGGACACAAAGG	ACG
rs1882510	AAACTGAGCTGGGCCTGC	ACT
rs1882511	GGGAGGCATTACAGGGATCA	ACG

Genetic Analysis

[0260] Allelotyping results from the discovery cohort are shown for cases and controls in Table 17. The allele frequency for the A2 allele is noted in the fifth and sixth columns for osteoarthritis case pools and control pools, respectively, where “AF” is allele frequency. The allele frequency for the A1 allele can be easily calculated by subtracting the A2 allele frequency from 1 ($A1\ AF = 1 - A2\ AF$). For example, the SNP rs3917304 has the following case and control allele frequencies: case A1 (G) = 0.431; case A2 (T) = 0.569; control A1 (G) = 0.450; and control A2 (T) = 0.550, where the nucleotide is provided in parenthesis. Some SNPs are labeled “untyped” because of failed assays.

TABLE 17

dbSNP rs#	Position in SEQ ID NO: 2	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3917304	225	102409525	G/T	0.569	0.550	0.460
rs2041747	509	102409809	C/T	0.027	0.023	0.800
rs3917305	860	102410160	C/T			
rs3771200	874	102410174	C/T	0.467	0.473	0.809
rs3917306	939	102410239	A/G			
rs3917307	1483	102410783	G/T			
rs3917308	1798	102411098	C/T			
rs3917310	2189	102411489	A/T			
rs3917311	2215	102411515	A/G	0.945	0.964	0.193
rs3917312	2282	102411582	C/G			
rs3917313	2340	102411640	C/T			
rs3917314	2963	102412263	A/C	0.025	0.028	0.881
rs3917316	3369	102412669	-/T	0.785	0.856	0.004
rs3171845	3481	102412781	A/G	0.904	0.894	0.624

dbSNP rs#	Position in SEQ ID NO: 2	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3171846	3564	102412864	G/T			
rs3917317	3653	102412953	-T/C	0.320	0.325	0.824
rs3917318	4860	102414160	A/G	0.151	0.151	0.978
rs3917319	4941	102414241	A/T			
rs3917320	4975	102414275	A/C	0.936	0.946	0.585
rs3917321	5321	102414621	A/G			
rs3917322	5346	102414646	A/G	0.978	untyped	NA
rs3917323	5541	102414841	A/G	0.977	untyped	NA
rs3917324	5633	102414933	C/G			
rs3917325	6007	102415307	G/T	0.029	0.030	0.901
rs3732134	6317	102415617	C/G			
rs3732133	6378	102415678	A/G			
rs2110726	6382	102415682	C/T	0.320	0.318	0.944
rs3917326	6426	102415726	C/T			
rs3917327	6479	102415779	C/G			
rs3917328	6641	102415941	C/T	0.898	0.891	0.706
rs3732131	6703	102416003	C/T	0.047	0.036	0.434
rs3732130	6705	102416005	C/T			
rs3917329	7963	102417263	G/T	0.070	0.081	0.473
rs3917330	8525	102417825	G/T			
rs3917331	8526	102417826	A/T			
rs3917344	8598	102417898	C/T			
rs3917332	8624	102417924	A/T	0.224	0.209	0.473
rs3917333	8883	102418183	A/T			
rs3917334	8980	102418280	G/T			
rs1030021	13578	102422878	G/T	0.160	0.183	0.255
rs2241132	16135	102425435	G/T	0.604	0.631	0.385
rs2241131	16141	102425441	G/T	0.451	0.477	0.282
rs3835036	16642	102425942	-T/GG	0.424	0.463	0.112
rs1997504	16931	102426231	A/G			
rs1805232	17004	102426304	A/G			
rs1971696	17009	102426309	C/T			
rs1971695	17010	102426310	A/G			
rs3771199	18713	102428013	C/T	0.299	0.291	0.726
rs1922303	18853	102428153	C/T			
rs3213734	20783	102430083	C/T	0.826	0.860	0.099
rs1997503	21335	102430635	A/G	0.830	0.806	0.281
rs1558649	22180	102431480	C/T			
rs1558648	22268	102431568	A/C	0.127	0.142	0.439
rs1558647	22285	102431585	C/T	0.824	0.825	0.955
rs1558646	25378	102434678	C/T	0.576	0.580	0.886
rs1882514	25906	102435206	C/G	0.547	0.556	0.730
rs1882513	26015	102435315	A/G	0.500	0.513	0.574
rs867770	26475	102435775	A/G			
rs2310235	26798	102436098	A/T	0.608	0.573	0.252
rs870684	27042	102436342	A/G	0.687	0.685	0.931
rs3771197	27649	102436949	A/G	0.534	0.544	0.676
rs3771196	27827	102437127	A/T	0.171	0.189	0.558
rs3821207	27873	102437173	A/G	0.029	0.033	0.751
rs3771195	28122	102437422	A/G	0.342	0.326	0.480
rs3771194	28202	102437502	A/G	0.474	0.465	0.725
rs3771193	28232	102437532	A/C			
rs3771192	28240	102437540	G/T			
rs3755290	29546	102438846	G/T	0.348	0.329	0.428
rs3821206	29748	102439048	A/G	0.914	0.920	0.803
rs2302623	30054	102439354	A/T	0.261	0.263	0.948
rs3755289	30646	102439946	G/T	0.429	0.442	0.621
rs1922302	31149	102440449	A/C	0.574	0.539	0.166
rs2110725	36912	102446212	A/C			
rs1465326	36936	102446236	C/G	0.592	0.613	0.413
rs2871458	37184	102446484	C/T	0.068	0.059	0.549
rs2080310	39064	102448364	C/T	0.258	0.256	0.926
rs1922289	39343	102448643	G/T	0.593	0.593	0.976

dbSNP rs#	Position in SEQ ID NO: 2	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1922290	40868	102450168	C/G	0.577	0.595	0.489
rs1922291	40917	102450217	A/G	0.344	0.358	0.549
rs1922292	41113	102450413	A/C	0.226	0.221	0.874
rs3815517	47343	102456643	A/T	0.291	0.291	0.984
rs2241130	47806	102457106	A/G	0.112	0.088	0.153
rs1922295	47911	102457211	A/G	0.362	0.349	0.594
rs1922294	48009	102457309	C/T	0.075	0.065	0.581
rs2302622	48621	102457921	C/G			
rs2310240	49245	102458545	C/G			
rs1024792	49247	102458547	C/G			
rs3836112	49299	102458599	-/CTCT	0.374	0.360	0.568
rs3074969	49302	102458602	-/AGAG	0.361	0.353	0.747
rs917994	49514	102458814	C/T	0.289	0.304	0.544
rs2041753	49626	102458926	G/T	0.330	0.329	0.981
rs2041752	49791	102459091	A/G	0.492	0.528	0.176
rs1024791	50010	102459310	A/G			
rs1024790	50294	102459594	A/G	0.771	0.776	0.828
rs995515	51482	102460782	A/G/T	0.312	0.310	0.917
rs995514	51556	102460856	A/G	0.393	0.420	0.246
rs1922293	51855	102461155	A/G	0.597	0.608	0.653
rs3755287	51956	102461256	C/T	0.869	0.885	0.458
rs3729564	52155	102461455	A/G	0.331	0.315	0.511
rs3771188	52448	102461748	A/G			
rs3771187	52458	102461758	C/T	0.280	0.258	0.332
rs3771186	52511	102461811	C/T	0.764	0.813	0.048
rs3771185	52607	102461907	A/G	0.429	0.395	0.160
rs2310241	54049	102463349	A/C	0.424	0.406	0.462
rs2302621	54224	102463524	A/C	0.323	0.340	0.473
rs2302620	54567	102463867	A/G	0.103	0.092	0.512
rs3771184	55052	102464352	C/T	0.779	0.809	0.173
rs3834161	55857	102465157	-/C	0.062	0.069	0.674
rs3755286	55941	102465241	C/G	0.786	0.817	0.150
rs3755285	56120	102465420	A/G	0.184	0.174	0.619
rs1997502	56349	102465649	C/T	0.580	0.564	0.559
rs3771182	56727	102466027	A/G	0.101	0.085	0.352
rs3836111	57232	102466532	-/CT	0.138	0.113	0.154
rs3771181	58806	102468106	C/T			
rs955754	61181	102470481	C/T	0.194	0.172	0.291
rs2302612	63808	102473108	A/G	0.135	0.120	0.456
rs3755284	64526	102473826	A/T	0.757	0.789	0.141
rs3821205	64865	102474165	A/G	0.831	0.832	0.992
rs3815511	64928	102474228	C/T	0.022	untyped	NA
rs2287041	64966	102474266	A/C	0.118	0.100	0.346
rs2287040	65080	102474380	A/G	0.518	0.536	0.462
rs2287039	65690	102474990	C/T	0.975	0.970	0.752
rs3755283	66228	102475528	A/G			
rs3755282	66982	102476282	A/G	0.312	0.295	0.452
rs1812326	72511	102481811	A/G	0.343	0.297	0.054
rs1558626	74170	102483470	A/T	0.536	0.551	0.643
rs1558625	74264	102483564	C/T	0.661	0.697	0.128
rs1558624	74333	102483633	C/T	0.322	0.278	0.074
rs1558623	74502	102483802	A/T	0.303	0.273	0.200
rs1035131	74741	102484041	A/C	0.543	0.595	0.046
rs2110661	75321	102484621	C/T	0.430	0.413	0.485
rs1420093	82558	102491858	A/G	0.381	0.388	0.826
rs3074971	85366	102494666	-/TTG	0.438	0.479	0.096
rs1345302	85469	102494769	C/T	0.428	0.397	0.223
rs1420092	86485	102495785	G/T	0.792	0.793	0.965
rs1345301	87687	102496987	C/T	0.514	0.477	0.131
rs2310242	89463	102498763	G/T	0.108	0.114	0.804
rs2310243	89660	102498960	A/G	0.490	0.523	0.194
rs1882510	95718	102505018	C/T	0.617	0.667	0.075
rs1882511	95821	102505121	A/G	0.664	0.652	0.599

[0261] The *IL1RL2* proximal SNPs were also allelotyped in the replication cohorts using the methods described herein and the primers provided in Tables 15 and 16. The replication allelotyping results for replication cohort #1 and replication cohort #2 are provided in Tables 18 and 19, respectively.

TABLE 18

dbSNP rs#	Position in SEQ ID NO: 2	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3917304	225	102409525	G/T	0.599	0.592	0.843
rs2041747	509	102409809	C/T	0.021	0.026	0.845
rs3917305	860	102410160	C/T			
rs3771200	874	102410174	C/T	0.442	0.482	0.207
rs3917306	939	102410239	A/G			
rs3917307	1483	102410783	G/T			
rs3917308	1798	102411098	C/T			
rs3917310	2189	102411489	A/T			
rs3917311	2215	102411515	A/G	0.933	0.974	0.042
rs3917312	2282	102411582	C/G			
rs3917313	2340	102411640	C/T			
rs3917314	2963	102412263	A/C	0.036	0.038	0.918
rs3917316	3369	102412669	-/T	0.904	0.963	0.072
rs3171845	3481	102412781	A/G	0.898	0.882	0.610
rs3171846	3564	102412864	G/T			
rs3917317	3653	102412953	-/TC	0.313	0.323	0.759
rs3917318	4860	102414160	A/G	0.149	0.142	0.803
rs3917319	4941	102414241	A/T			
rs3917320	4975	102414275	A/C	0.921	0.930	0.749
rs3917321	5321	102414621	A/G			
rs3917322	5346	102414646	A/G			
rs3917323	5541	102414841	A/G			
rs3917324	5633	102414933	C/G			
rs3917325	6007	102415307	G/T	0.033	0.040	0.716
rs3732134	6317	102415617	C/G			
rs3732133	6378	102415678	A/G			
rs2110726	6382	102415682	C/T	0.334	0.339	0.880
rs3917326	6426	102415726	C/T			
rs3917327	6479	102415779	C/G			
rs3917328	6641	102415941	C/T	0.885	0.867	0.523
rs3732131	6703	102416003	C/T	0.045	0.022	0.224
rs3732130	6705	102416005	C/T			
rs3917329	7963	102417263	G/T	0.068	0.091	0.296
rs3917330	8525	102417825	G/T			
rs3917331	8526	102417826	A/T			
rs3917344	8598	102417898	C/T			
rs3917332	8624	102417924	A/T	0.203	0.195	0.785
rs3917333	8883	102418183	A/T			
rs3917334	8980	102418280	G/T			
rs1030021	13578	102422878	G/T	0.148	0.174	0.325
rs2241132	16135	102425435	G/T	0.604	0.595	0.815
rs2241131	16141	102425441	G/T	0.452	0.464	0.696
rs3835036	16642	102425942	-/TGG	0.402	0.479	0.017
rs1997504	16931	102426231	A/G			
rs1805232	17004	102426304	A/G			
rs1971696	17009	102426309	C/T			
rs1971695	17010	102426310	A/G			
rs3771199	18713	102428013	C/T	0.317	0.310	0.818
rs1922303	18853	102428153	C/T			
rs3213734	20783	102430083	C/T	0.824	0.892	0.012
rs1997503	21335	102430635	A/G	0.838	0.790	0.114

dbSNP rs#	Position in SEQ ID NO: 2	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1558649	22180	102431480	C/T			
rs1558648	22268	102431568	A/C	0.125	0.164	0.121
rs1558647	22285	102431585	C/T	0.834	0.831	0.895
rs1558646	25378	102434678	C/T	0.547	0.561	0.672
rs1882514	25906	102435206	C/G	0.538	0.542	0.905
rs1882513	26015	102435315	A/G	0.471	0.497	0.414
rs867770	26475	102435775	A/G			
rs2310235	26798	102436098	A/T	0.562	NA	0.608
rs870684	27042	102436342	A/G	0.657	0.680	0.509
rs3771197	27649	102436949	A/G	0.502	0.534	0.351
rs3771196	27827	102437127	A/T	0.171	0.189	0.558
rs3821207	27873	102437173	A/G	0.033	0.038	0.821
rs3771195	28122	102437422	A/G	0.374	0.342	0.311
rs3771194	28202	102437502	A/G	0.493	0.480	0.696
rs3771193	28232	102437532	A/C			
rs3771192	28240	102437540	G/T			
rs3755290	29546	102438846	G/T	0.364	0.346	0.602
rs3821206	29748	102439048	A/G	0.940	NA	0.914
rs2302623	30054	102439354	A/T	0.267	0.268	0.984
rs3755289	30646	102439946	G/T	0.417	0.451	0.281
rs1922302	31149	102440449	A/C	0.600	0.559	0.245
rs2110725	36912	102446212	A/C			
rs1465326	36936	102446236	C/G	0.573	0.614	0.296
rs2871458	37184	102446484	C/T	0.085	0.070	0.530
rs2080310	39064	102448364	C/T	0.277	0.268	0.776
rs1922289	39343	102448643	G/T	0.580	0.576	0.924
rs1922290	40868	102450168	C/G	0.558	0.579	0.556
rs1922291	40917	102450217	A/G	0.322	0.348	0.401
rs1922292	41113	102450413	A/C	0.235	untyped	NA
rs3815517	47343	102456643	A/T	0.310	0.312	0.950
rs2241130	47806	102457106	A/G	0.110	0.068	0.071
rs1922295	47911	102457211	A/G	0.378	0.364	0.695
rs1922294	48009	102457309	C/T	0.061	0.055	0.799
rs2302622	48621	102457921	C/G			
rs2310240	49245	102458545	C/G			
rs1024792	49247	102458547	C/G			
rs3836112	49299	102458599	-/CTCT	0.407	0.378	0.382
rs3074969	49302	102458602	-/AGAG	0.385	0.362	0.497
rs917994	49514	102458814	C/T	0.271	0.281	0.757
rs2041753	49626	102458926	G/T	0.357	0.342	0.672
rs2041752	49791	102459091	A/G	0.459	0.511	0.155
rs1024791	50010	102459310	A/G			
rs1024790	50294	102459594	A/G	0.781	0.773	0.769
rs995515	51482	102460782	A/G/T	0.331	0.323	0.825
rs995514	51556	102460856	A/G	0.373	0.412	0.221
rs1922293	51855	102461155	A/G	0.568	0.597	0.376
rs3755287	51956	102461256	C/T	0.867	0.907	0.138
rs3729564	52155	102461455	A/G	0.362	0.320	0.212
rs3771188	52448	102461748	A/G			
rs3771187	52458	102461758	C/T	0.308	0.276	0.288
rs3771186	52511	102461811	C/T	0.761	0.847	0.003
rs3771185	52607	102461907	A/G	0.445	0.385	0.069
rs2310241	54049	102463349	A/C	0.446	0.400	0.161
rs2302621	54224	102463524	A/C	0.304	0.326	0.499
rs2302620	54567	102463867	A/G	0.100	0.074	0.236
rs3771184	55052	102464352	C/T	0.785	0.853	0.014
rs3834161	55857	102465157	-/C	0.068	0.081	0.596
rs3755286	55941	102465241	C/G	0.791	0.850	0.038
rs3755285	56120	102465420	A/G	0.194	0.173	0.446
rs1997502	56349	102465649	C/T	0.604	0.577	0.536
rs3771182	56727	102466027	A/G	0.107	0.070	0.117
rs3836111	57232	102466532	-/CT	0.137	0.090	0.048
rs3771181	58806	102468106	C/T			

dbSNP rs#	Position in SEQ ID NO: 2	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs955754	61181	102470481	C/T	0.209	0.160	0.084
rs2302612	63808	102473108	A/G	0.138	0.111	0.331
rs3755284	64526	102473826	A/T	0.754	0.829	0.010
rs3821205	64865	102474165	A/G	0.799	0.814	0.594
rs3815511	64928	102474228	C/T			
rs2287041	64966	102474266	A/C	0.113	0.074	0.143
rs2287040	65080	102474380	A/G	0.493	0.521	0.386
rs2287039	65690	102474990	C/T	0.970	0.962	0.703
rs3755283	66228	102475528	A/G			
rs3755282	66982	102476282	A/G	0.327	0.312	0.636
rs1812326	72511	102481811	A/G	0.362	0.299	0.067
rs1558626	74170	102483470	A/T	0.558	untyped	
rs1558625	74264	102483564	C/T	0.635	0.683	0.137
rs1558624	74333	102483633	C/T	0.350	0.278	0.024
rs1558623	74502	102483802	A/T	0.323	0.281	0.204
rs1035131	74741	102484041	A/C	0.513	0.598	0.026
rs2110661	75321	102484621	C/T	0.449	0.412	0.237
rs1420093	82558	102491858	A/G	0.390	untyped	
rs3074971	85366	102494666	-TTG	0.398	0.485	0.006
rs1345302	85469	102494769	C/T	0.468	0.392	0.036
rs1420092	86485	102495785	G/T	0.810	0.808	0.958
rs1345301	87687	102496987	C/T	0.554	0.470	0.016
rs2310242	89463	102498763	G/T	0.110	untyped	
rs2310243	89660	102498960	A/G	0.452	0.529	0.031
rs1882510	95718	102505018	C/T	0.597	0.688	0.022
rs1882511	95821	102505121	A/G	0.684	0.657	0.373

TABLE 19

dbSNP rs#	Position in Figure 2	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3917304	225	102409525	G/T	0.531	0.483	0.236
rs2041747	509	102409809	C/T	0.034	untyped	
rs3917305	860	102410160	C/T			
rs3771200	874	102410174	C/T	0.500	0.460	0.282
rs3917306	939	102410239	A/G			
rs3917307	1483	102410783	G/T			
rs3917308	1798	102411098	C/T			
rs3917310	2189	102411489	A/T			
rs3917311	2215	102411515	A/G	0.959	0.947	0.574
rs3917312	2282	102411582	C/G			
rs3917313	2340	102411640	C/T			
rs3917314	2963	102412263	A/C			
rs3917316	3369	102412669	-T	0.633	0.687	0.176
rs3171845	3481	102412781	A/G	0.912	0.913	0.964
rs3171846	3564	102412864	G/T			
rs3917317	3653	102412953	-TC	0.329	0.329	0.999
rs3917318	4860	102414160	A/G	0.153	0.165	0.696
rs3917319	4941	102414241	A/T			
rs3917320	4975	102414275	A/C	0.955	0.971	0.463
rs3917321	5321	102414621	A/G			
rs3917322	5346	102414646	A/G			
rs3917323	5541	102414841	A/G			
rs3917324	5633	102414933	C/G			
rs3917325	6007	102415307	G/T	0.023	untyped	
rs3732134	6317	102415617	C/G			
rs3732133	6378	102415678	A/G			
rs2110726	6382	102415682	C/T	0.301	0.285	0.632
rs3917326	6426	102415726	C/T			
rs3917327	6479	102415779	C/G			
rs3917328	6641	102415941	C/T	0.915	0.929	0.621

dbSNP rs#	Position in Figure 2	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3732131	6703	102416003	C/T	0.049	0.058	0.670
rs3732130	6705	102416005	C/T			
rs3917329	7963	102417263	G/T	0.073	0.067	0.798
rs3917330	8525	102417825	G/T			
rs3917331	8526	102417826	A/T			
rs3917344	8598	102417898	C/T			
rs3917332	8624	102417924	A/T	0.251	0.231	0.534
rs3917333	8883	102418183	A/T			
rs3917334	8980	102418280	G/T			
rs1030021	13578	102422878	G/T	0.176	0.197	0.489
rs2241132	16135	102425435	G/T	untyped	0.688	NA
rs2241131	16141	102425441	G/T	0.451	0.498	0.204
rs3835036	16642	102425942	-/TGG	0.453	0.439	0.715
rs1997504	16931	102426231	A/G			
rs1805232	17004	102426304	A/G			
rs1971696	17009	102426309	C/T			
rs1971695	17010	102426310	A/G			
rs3771199	18713	102428013	C/T	0.277	0.262	0.665
rs1922303	18853	102428153	C/T			
rs3213734	20783	102430083	C/T	0.827	0.809	0.573
rs1997503	21335	102430635	A/G	0.821	0.832	0.740
rs1558649	22180	102431480	C/T			
rs1558648	22268	102431568	A/C	0.130	0.105	0.368
rs1558647	22285	102431585	C/T	0.810	0.815	0.861
rs1558646	25378	102434678	C/T	0.613	0.608	0.893
rs1882514	25906	102435206	C/G	0.558	0.578	0.630
rs1882513	26015	102435315	A/G	0.537	0.539	0.952
rs867770	26475	102435775	A/G			
rs2310235	26798	102436098	A/T	0.589	0.019	
rs870684	27042	102436342	A/G	0.726	0.693	0.392
rs3771197	27649	102436949	A/G	0.574	0.561	0.725
rs3771196	27827	102437127	A/T			
rs3821207	27873	102437173	A/G	0.023	0.026	0.884
rs3771195	28122	102437422	A/G	0.303	0.301	0.952
rs3771194	28202	102437502	A/G	0.450	0.442	0.832
rs3771193	28232	102437532	A/C			
rs3771192	28240	102437540	G/T			
rs3755290	29546	102438846	G/T	0.328	0.302	0.452
rs3821206	29748	102439048	A/G	0.889	0.026	
rs2302623	30054	102439354	A/T	0.254	0.255	0.962
rs3755289	30646	102439946	G/T	0.444	0.429	0.744
rs1922302	31149	102440449	A/C	0.541	0.507	0.364
rs2110725	36912	102446212	A/C			
rs1465326	36936	102446236	C/G	0.616	0.612	0.919
rs2871458	37184	102446484	C/T	0.046	0.041	0.775
rs2080310	39064	102448364	C/T	0.235	0.238	0.933
rs1922289	39343	102448643	G/T	0.611	0.618	0.845
rs1922290	40868	102450168	C/G	0.601	0.619	0.631
rs1922291	40917	102450217	A/G	0.372	0.374	0.961
rs1922292	41113	102450413	A/C	0.215	0.221	0.827
rs3815517	47343	102456643	A/T	0.268	0.257	0.766
rs2241130	47806	102457106	A/G	0.115	0.119	0.854
rs1922295	47911	102457211	A/G	0.342	0.325	0.632
rs1922294	48009	102457309	C/T	0.092	0.081	0.677
rs2302622	48621	102457921	C/G			
rs2310240	49245	102458545	C/G			
rs1024792	49247	102458547	C/G			
rs3836112	49299	102458599	-/CTCT	0.332	0.332	0.999
rs3074969	49302	102458602	-/AGAG	0.330	0.339	0.822
rs917994	49514	102458814	C/T	0.312	0.339	0.456
rs2041753	49626	102458926	G/T	0.296	0.310	0.737
rs2041752	49791	102459091	A/G	0.534	0.556	0.587
rs1024791	50010	102459310	A/G			
rs1024790	50294	102459594	A/G	0.759	0.780	0.498

dbSNP rs#	Position in Figure 2	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- V alue
rs995515	51482	102460782	A/G/T	0.288	0.288	0.992
rs995514	51556	102460856	A/G	0.417	0.434	0.657
rs1922293	51855	102461155	A/G	0.634	0.625	0.806
rs3755287	51956	102461256	C/T	0.873	0.850	0.471
rs3729564	52155	102461455	A/G	0.291	0.308	0.643
rs3771188	52448	102461748	A/G			
rs3771187	52458	102461758	C/T	0.246	0.231	0.677
rs3771186	52511	102461811	C/T	0.766	0.759	0.850
rs3771185	52607	102461907	A/G	0.409	0.410	0.972
rs2310241	54049	102463349	A/C	0.396	0.416	0.591
rs2302621	54224	102463524	A/C	0.347	0.363	0.667
rs2302620	54567	102463867	A/G	0.107	0.121	0.605
rs3771184	55052	102464352	C/T	0.772	0.740	0.364
rs3834161	55857	102465157	-/C	0.054	0.051	0.860
rs3755286	55941	102465241	C/G	0.781	0.766	0.641
rs3755285	56120	102465420	A/G	0.172	0.175	0.897
rs1997502	56349	102465649	C/T	0.550	0.543	0.849
rs3771182	56727	102466027	A/G	0.094	0.109	0.562
rs3836111	57232	102466532	-/CT	0.139	0.148	0.750
rs3771181	58806	102468106	C/T			
rs955754	61181	102470481	C/T	0.173	0.190	0.571
rs2302612	63808	102473108	A/G	0.132	0.135	0.909
rs3755284	64526	102473826	A/T	0.760	0.726	0.332
rs3821205	64865	102474165	A/G	0.873	0.859	0.629
rs3815511	64928	102474228	C/T			
rs2287041	64966	102474266	A/C	0.124	0.141	0.517
rs2287040	65080	102474380	A/G	0.550	0.559	0.802
rs2287039	65690	102474990	C/T			
rs3755283	66228	102475528	A/G			
rs3755282	66982	102476282	A/G	0.293	0.268	0.452
rs1812326	72511	102481811	A/G	0.320	0.294	0.453
rs1558626	74170	102483470	A/T	0.541	untyped	
rs1558625	74264	102483564	C/T	0.694	0.719	0.473
rs1558624	74333	102483633	C/T	0.285	0.279	0.865
rs1558623	74502	102483802	A/T	0.277	0.261	0.615
rs1035131	74741	102484041	A/C	0.581	0.590	0.795
rs2110661	75321	102484621	C/T	0.405	0.414	0.800
rs1420093	82558	102491858	A/G	0.384	untyped	
rs3074971	85366	102494666	-/TTG	0.488	0.469	0.619
rs1345302	85469	102494769	C/T	0.378	0.406	0.437
rs1420092	86485	102495785	G/T	0.769	0.768	0.980
rs1345301	87687	102496987	C/T	0.464	0.487	0.531
rs2310242	89463	102498763	G/T	0.120	untyped	
rs2310243	89660	102498960	A/G	0.537	0.514	0.548
rs1882510	95718	102505018	C/T	0.642	0.635	0.875
rs1882511	95821	102505121	A/G	0.639	0.644	0.871

[0262] Allelotyping results were considered particularly significant with a calculated **p**-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The allelotyping **p**-values were plotted in Figure 1B for the discovery cohort. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the **p**-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figure 1B can be determined by consulting Table 17. For example, the left-most X on the left graph is at

position 102409525. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0263] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The generally bottom-most curve is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0264] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is placed at the 3' end of each gene to show the direction of transcription.

Example 6

IL1RL1 Region Proximal SNPs

[0265] It has been discovered that SNP rs1041973 in Interleukin 1 receptor-like 1 isoform 1 (*IL1RL1*) is associated with occurrence of osteoarthritis in subjects. Interleukin 1 receptor-like 1 isoform 1 is a member of the interleukin 1 receptor family with no known ligand (orphan receptor). *IL1RL1* exists in both a soluble and transmembrane form, suggesting that it may have ligand and scavenging activity. Studies of the similar gene in mouse suggested that this receptor can be induced by proinflammatory stimuli. This gene and four other interleukin 1 receptor family genes, including interleukin 1 receptor, type I (IL1R1), interleukin 1 receptor, type II (IL1R2), interleukin 1 receptor-like 2 (IL1RL2), and interleukin 18 receptor 1 (IL18R1), form a cytokine receptor gene cluster.

[0266] Ninety-one additional allelic variants proximal to rs1041973 were identified and subsequently allelotyped in osteoarthritis case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 20. The chromosome positions provided in column four of Table 20 are based on Genome "Build 34" of NCBI's GenBank.

TABLE 20

dbSNP rs#	Chromosome	Position in SEQ ID NO: 4	Chromosome Position	Allele Variants
rs884517	2	207	102527857	c/t
rs1476984	2	6019	102533669	a/g

dbSNP rs#	Chromosome	Position in SEQ ID NO: 4	Chromosome Position	Allele Variants
rs951774	2	6414	102534064	a/c
rs2041737	2	7341	102534991	a/g
rs1420091	2	10984	102538634	a/g
rs2110660	2	12351	102540001	c/g
rs1362347	2	13335	102540985	a/g
rs3073968	2	16584	102544234	-/tgtg/tgtgag
rs4090473	2	16737	102544387	c/g
rs1558622	2	23897	102551547	c/t
rs1558621	2	24057	102551707	c/t
rs1558620	2	25145	102552795	a/g
rs1558619	2	25300	102552950	a/c
rs950881	2	26262	102553912	a/c
rs950880	2	26312	102553962	g/t
rs1362346	2	26589	102554239	c/t
rs1968171	2	27302	102554952	a/g
rs1813299	2	27358	102555008	a/t
rs1813298	2	27451	102555101	c/g
rs1968170	2	27552	102555202	c/t
rs974389	2	30731	102558381	c/t
rs971764	2	32085	102559735	a/g
rs1420089	2	32139	102559789	a/g
rs1420088	2	33184	102560834	a/g
rs1420103	2	42382	102570032	g/t
rs1420102	2	42569	102570219	a/g
rs1997467	2	44823	102572473	c/t
rs1997466	2	45217	102572867	c/g
rs1362350	2	45548	102573198	c/g
rs2310220	2	45601	102573251	a/g
rs1362349	2	45722	102573372	c/g
rs3755278	2	45967	102573617	a/g
rs3771180	2	47367	102575017	a/c
rs3771179	2	47642	102575292	a/c
rs985523	2	48126	102575776	c/t
rs1041973	2	49218	102576868	a/c
rs3214363	2	49274	102576924	-/a
rs873022	2	49433	102577083	g/t
rs3771177	2	49610	102577260	a/c
rs3732129	2	51282	102578932	a/g
rs1420101	2	51466	102579116	a/g
rs12905	2	53757	102581407	a/g
rs3771175	2	53960	102581610	a/t
rs3821204	2	54031	102581681	c/g
rs2160203	2	54574	102582224	c/t
rs1946131	2	55679	102583329	a/g
rs1054096	2	56100	102583750	c/t
rs2287038	2	56182	102583832	c/t
rs1921622	2	59817	102587467	a/g
rs1861246	2	60533	102588183	a/g
rs1861245	2	60656	102588306	a/g
rs3755276	2	72209	102599859	a/g
rs2287037	2	72778	102600428	a/g
rs1420099	2	74293	102601943	c/g

dbSNP rs#	Chromosome	Position in SEQ ID NO: 4	Chromosome Position	Allele Variants
rs3771174	2	77335	102604985	a/g
rs1420098	2	78029	102605679	a/g
rs1362348	2	78374	102606024	c/g
rs1882348	2	78421	102606071	a/t
rs1558627	2	78434	102606084	c/t
rs2058622	2	79174	102606824	c/t
rs3836110	2	79397	102607047	-/g
rs3771172	2	79562	102607212	a/g
rs3771171	2	79700	102607350	a/g
rs3771170	2	79730	102607380	a/t
rs2160202	2	79904	102607554	c/t
rs2058623	2	79920	102607570	a/g
rs3771167	2	79938	102607588	c/t
rs3771166	2	79972	102607622	c/t
rs1974675	2	80125	102607775	c/t
rs1465321	2	80368	102608018	a/g
rs2041740	2	83484	102611134	c/t
rs3771164	2	85536	102613186	a/t
rs2270298	2	85829	102613479	c/t
rs2270297	2	86425	102614075	a/g
rs2041739	2	88083	102615733	a/g
rs2080289	2	88770	102616420	c/t
rs3821203	2	90622	102618272	a/g
rs3771162	2	90924	102618574	a/t
rs3213733	2	91634	102619284	g/t
rs3213732	2	92029	102619679	c/t
rs1035130	2	95152	102622802	a/g
rs3752659	2	95348	102622998	c/t
rs3755274	2	96145	102623795	c/t
rs2241117	2	96793	102624443	a/g
rs2241116	2	97015	102624665	g/t
rs881890	2	97064	102624714	c/t
rs3771161	2	97711	102625361	g/t
rs3771160	2	97855	102625505	a/c
rs3771159	2	98708	102626358	a/g
rs1420104	2	not mapped	not mapped	c/t
rs2041738	2	not mapped	not mapped	a/c

Assay for Verifying and Allelotyping SNPs

[0267] The methods used to verify and allelotype the 91 proximal SNPs of Table 20 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 21 and Table 22, respectively.

TABLE 21

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs884517	ACGTTGGATGCATTTTCTGGTGTGACTCCC	ACGTTGGATGATGTTCCGGTCACCTTGTGAGC
rs1476984	ACGTTGGATGTGAGAGAGTTGAAGAATGGG	ACGTTGGATGCCAAGAAGTGATTTCTTCC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs951774	ACGTTGGATGTCAGCCAGAGGTCTTTACTC	ACGTTGGATGTTAGAAGTCTCTTGGGTGGG
rs2041737	ACGTTGGATGGAGATGGAGTTTCCCTCTTG	ACGTTGGATGAAACCAAGAGGTGGAGGTTG
rs1420091	ACGTTGGATGCACCCCTATTATAAAACCCAC	ACGTTGGATGACCAGAAATGGCATCTATGG
rs2110660	ACGTTGGATGTCTCTCCGAGATGAGGAATC	ACGTTGGATGGTGATCTCCTCAGTACTCTG
rs1362347	ACGTTGGATGTTCTTTGGTAATGAGGTAGG	ACGTTGGATGTGCTTGCCCTCTATTATGG
rs3073968	ACGTTGGATGGAATGATGAGGAAGGAAGGG	ACGTTGGATGTAAAGCCACATGTTACCCCG
rs4090473	ACGTTGGATGTAGTGTGTTTCACTCTTCCC	ACGTTGGATGTCAAGCACCTCTGTAACTC
rs1558622	ACGTTGGATGATACTTCCTGGTTTTCTGGG	ACGTTGGATGGGCTCAAAGTCATCACCCAA
rs1558621	ACGTTGGATGACAGTGGCGATGCCAACATT	ACGTTGGATGCCTGTAGTAGGACCCTACTG
rs1558620	ACGTTGGATGTTGCAGGTGTCTGGTGATAG	ACGTTGGATGAGTTGCCTTTCTTCATGGC
rs1558619	ACGTTGGATGCCCTAATTAGGATTCCGCAC	ACGTTGGATGCTCCATCACACTTTGACTGC
rs950881	ACGTTGGATGCTTATCTCAGTCTGCCAGTG	ACGTTGGATGGGTGAGTGAATTAGTCCTGG
rs950880	ACGTTGGATGTGCCAAAGACAATCAAATCC	ACGTTGGATGCACTCACCTCTGATTTCTAG
rs1362346	ACGTTGGATGTTCTCAGGTTACCAAGAG	ACGTTGGATGTCCCGAACCTCATCTCATAC
rs1968171	ACGTTGGATGAATGTTTCAGCCAGCATGG	ACGTTGGATGATCTCCTGACCTCATGATCC
rs1813299	ACGTTGGATGAATTCAGCACCTTTGGGAGG	ACGTTGGATGTTTACCCTGTTAGCCAGGA
rs1813298	ACGTTGGATGTTACTGCAAGCTCCACCTCC	ACGTTGGATGATTAAGTGGGCGTGGTGGTG
rs1968170	ACGTTGGATGAGCTTGCAGTAAGCCCAGAT	ACGTTGGATGTGTTAGGGTAATTACAGTGC
rs974389	ACGTTGGATGCTCTAGCCCAATATGTCTCC	ACGTTGGATGACTGGAGATGTGAACCCATC
rs971764	ACGTTGGATGGAGATGATGGAGATTAAGAGG	ACGTTGGATGAGTTGTTTGACTTCGGACTG
rs1420089	ACGTTGGATGAGACAGCACATATCAATGAC	ACGTTGGATGTATTGTGCGGTTTCGCTATAG
rs1420088	ACGTTGGATGGGATGACTGTCAAAAACATC	ACGTTGGATGTAATTTTCAGGAGCAAGGC
rs1420103	ACGTTGGATGTCCATTGGAATATGACCTCC	ACGTTGGATGCCAGGCACATGAGCTATATC
rs1420102	ACGTTGGATGGATTGGTCAGGAACTCAAAC	ACGTTGGATGTGGGTTGCTTCTAGCTATTG
rs1997467	ACGTTGGATGTGAATTTAGTGAGTCAGGC	ACGTTGGATGTGAGGGGAAAAAACAATCC
rs1997466	ACGTTGGATGATAGGCACATACAGGATTC	ACGTTGGATGCTCCCTTTTCAGATTAATCTC
rs1362350	ACGTTGGATGGGAGAACATTCTCTATACCAG	ACGTTGGATGTGCCTGAATAGTGAGAAGCC
rs2310220	ACGTTGGATGGGTTGAAACCAGACTTGCTG	ACGTTGGATGCAGCCTAATCTCTGGTATAG
rs1362349	ACGTTGGATGCAATACTCTGTGGTACTTATC	ACGTTGGATGTAAACAGTCTTATCCTTGGG
rs3755278	ACGTTGGATGAGTGCTGAATAGGTTTGTTT	ACGTTGGATGGCCTAGTTTAAGAATGAATGC
rs3771180	ACGTTGGATGGTCAACATCAAGAATTCCTAG	ACGTTGGATGCCTGAAATTTGATTTGTGGC
rs3771179	ACGTTGGATGGTCTTCATAATTCATGATTG	ACGTTGGATGTCTTAAATATAAGGGGAAG
rs985523	ACGTTGGATGTCTATGGAAGTTTGGGTC	ACGTTGGATGCTGCGAAGTAGCATGATAAC
rs1041973	ACGTTGGATGGGGACTTCTGACAATACAGG	ACGTTGGATGAATCGTGTGTTTGCCTCAGG
rs3214363	ACGTTGGATGCAGGCAATCAACCACTGAAG	ACGTTGGATGCTGCAGTTGCTGATTCTGGT
rs873022	ACGTTGGATGCCTAGTCCTTTCTGGAACAG	ACGTTGGATGATCCCTGCAACTGTAAATCC
rs3771177	ACGTTGGATGAAGGTTAGAAGCCCCTTTTC	ACGTTGGATGGGCTGGAATTAAGAACAAC
rs3732129	ACGTTGGATGCTAATTCAAAGCCACATCTG	ACGTTGGATGTAAGTTAGCATTAGATTGC
rs1420101	ACGTTGGATGCAACATTTATGTACACCATAG	ACGTTGGATGTTAGTAATACTCATTGGATT
rs12905	ACGTTGGATGCTCCAGCAAACAGGAACAG	ACGTTGGATGATCAAGACAATGGGAATGGC
rs3771175	ACGTTGGATGAAAGAGCACAAAAGAACACG	ACGTTGGATGTTATGAACTCCCTCTGTGTC
rs3821204	ACGTTGGATGCATGTTGTAAGCATGGTCCG	ACGTTGGATGACTTTACCACCCTCGCTAAC
rs2160203	ACGTTGGATGACACAGACCCAAACCATACC	ACGTTGGATGTTCCCGTGTGTTCCATGTAC
rs1946131	ACGTTGGATGGGGAACCTCAGGGTTTAACAC	ACGTTGGATGTACACTCATCACTCCTCAGG
rs1054096	ACGTTGGATGATCAAGGTGCTATGTGAGGG	ACGTTGGATGAAAGCAGGAGTACACAAGGG
rs2287038	ACGTTGGATGAATGTCCCTGGTTACCTATG	ACGTTGGATGACAAATAAGCTAGAAGGAGC
rs1921622	ACGTTGGATGGCCACTTCTTAATTCTGTCC	ACGTTGGATGATTTTCACTAGTGCCTATGG
rs1861246	ACGTTGGATGCACAAGCTCTTCACCTCTTC	ACGTTGGATGTGGCTGAGGAGAAGTGTAAC
rs1861245	ACGTTGGATGTGCTGCCTTCAATGTGTGAC	ACGTTGGATGAGGAAAGGTGAGAGGACATG
rs3755276	ACGTTGGATGCCAGCACTCACTAACATGTG	ACGTTGGATGAAACTCATATGGGCAGCCAC
rs2287037	ACGTTGGATGCAGATTCAGCCAAAGCTTTC	ACGTTGGATGAAAAATCTGTGTGCCAGAAG
rs1420099	ACGTTGGATGTTACACACTCTCCAGAGGTG	ACGTTGGATGAAAGCTTCTAGCTGCCTGAG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs3771174	ACGTTGGATGACCCAGATTCTCTGGCTTTG	ACGTTGGATGTACCACAAGTGCCGAAAGAG
rs1420098	ACGTTGGATGGGGACGTGAAGTACAAGAT	ACGTTGGATGGGAGACCAAAAAAAGTTACC
rs1362348	ACGTTGGATGCATGTCATAGGAAGAGTAGG	ACGTTGGATGTCAGCAACTCAAATATGCAG
rs1882348	ACGTTGGATGCCTACTCTTCCTATGACATG	ACGTTGGATGCCCTAAAAGGAAATCCTATC
rs1558627	ACGTTGGATGCCCTAAAAGGAAATCCTATC	ACGTTGGATGCCTACTCTTCCTATGACATG
rs2058622	ACGTTGGATGCTGTGAAACCTTGGTAGCAC	ACGTTGGATGTTTCTGATGCCTGGGAGTTC
rs3836110	ACGTTGGATGACTCACAAATGGGGTAAAGG	ACGTTGGATGTGCCTTCATTCAATCAGGAG
rs3771172	ACGTTGGATGCAGAAGCAAATGGCATTGGC	ACGTTGGATGCCATTGTTGCTTCCTAAGCC
rs3771171	ACGTTGGATGAGGGTAGCAGATAGGAGATG	ACGTTGGATGAAGCTGCTTCTCTCCTCATC
rs3771170	ACGTTGGATGCAAGGCCATTGTCAAAGCTG	ACGTTGGATGGTGTCCCAGAGTGGATATTG
rs2160202	ACGTTGGATGAGCAGTATTTACTGCAGATG	ACGTTGGATGCCACATCAAAGTCAAAGG
rs2058623	ACGTTGGATGATTTACTGCAGATGTGTGTG	ACGTTGGATGTGTTCACTGATAGATCCAC
rs3771167	ACGTTGGATGCTAACTTAAGTGTGTAACCC	ACGTTGGATGCTAACGGGAAATTTTCAGGTG
rs3771166	ACGTTGGATGGTGAACAGACTTTACACCTG	ACGTTGGATGCCTCAGTGGCATTGATTAT
rs1974675	ACGTTGGATGACTAAGAAGGAAGGGGATAC	ACGTTGGATGGTACATTTCCCTCTACCTTC
rs1465321	ACGTTGGATGTCACAGCTTTGGGTCAGTTG	ACGTTGGATGTCAACAACACACTGCACCTG
rs2041740	ACGTTGGATGCATCCATGTCCCTACAAAAG	ACGTTGGATGAAAGCTCTTATACACCATGG
rs3771164	ACGTTGGATGCCTGTGACATGTATGGAAATG	ACGTTGGATGTCAAATCCATAGGTACACTC
rs2270298	ACGTTGGATGTGAAGTAGTGTCTCTCTC	ACGTTGGATGAATATGAGCACTGTAGCTGC
rs2270297	ACGTTGGATGTTTCTGCCAAAAAGAAAGG	ACGTTGGATGGACCACACCACTAGTTCAA
rs2041739	ACGTTGGATGTAGACCCTGAAGTTTCCAC	ACGTTGGATGCACCTAGAGGTTCTTTTGC
rs2080289	ACGTTGGATGTGGAGAATGTCAACTGAGTC	ACGTTGGATGATACAAACAAGAGGCCATGG
rs3821203	ACGTTGGATGTCAAAGACAAAGGGCAGGAG	ACGTTGGATGGGATCCAGAGAAAGGTAGTC
rs3771162	ACGTTGGATGTGAGTGGAGTACAGTGAGAC	ACGTTGGATGTGGCACTGCACTTTCTGAGA
rs3213733	ACGTTGGATGTGAAAGCACCTTGTATCTGG	ACGTTGGATGCATCTTCTCTGCCTTTTAG
rs3213732	ACGTTGGATGGTCAGGTTAAAAGTGGCAAC	ACGTTGGATGTGACACTGGATACACATTTT
rs1035130	ACGTTGGATGTTAGGATCCGATCCATTTTC	ACGTTGGATGCTCTGCTTTGCTGAATGAAG
rs3752659	ACGTTGGATGTGCATAATGCGTCCACCTAG	ACGTTGGATGGGCTGATGTGTATTTGGGC
rs3755274	ACGTTGGATGTATCAAAGGTGTGTGCACCC	ACGTTGGATGAGGGGTAGAAAACCAAGTG
rs2241117	ACGTTGGATGTGGCTGGAAGATCATGATGC	ACGTTGGATGCCCCAAGTTGTTAGGAAGAG
rs2241116	ACGTTGGATGAATGCAGGCAACATCACAGC	ACGTTGGATGAGTAGGCTCTGTTCTGTTACC
rs881890	ACGTTGGATGATGCCATTTGCCTTCTGGAG	ACGTTGGATGTCTCAGGGTAACGAACAGAG
rs3771161	ACGTTGGATGCCATCAGGTGAGCACTGAAA	ACGTTGGATGTCATTGCCTCCTGAACCTGG
rs3771160	ACGTTGGATGAGAAATGGCTGTGACTGGAG	ACGTTGGATGTATCCAGGGAGTTGATGGTG
rs3771159	ACGTTGGATGCAGGTGATGGTCCAACAAAG	ACGTTGGATGTGCTGTGGTCCACTCACTTG
rs1420104	ACGTTGGATGTATTCTGGAGGCTGAGGTGG	ACGTTGGATGTGGAGTGCAGTGGTGTGATC
rs2041738	ACGTTGGATGTGGTGAACCCCATCTCTAC	ACGTTGGATGTTTCAAGCTATTCTCCTGCC

TABLE 22

dbSNP rs#	Extend Primer	Term Mix
rs884517	GGTGTGACTCCCAGACCAA	ACT
rs1476984	ATGGGTAGTTAATGGTGGAAATTT	ACT
rs951774	CAAAGTAGTTGACTTGTCTTTCT	ACT
rs2041737	CCAGGCTAGTGCAGTGGC	ACT
rs1420091	CCCACATTATATTGTCATTACTTT	ACG
rs2110660	ATGAGGAATCAGAGCTGGGA	ACT
rs1362347	GTAATGAGGTAGGAATAATATTG	ACT
rs3073968	GGCAATTGTGTGTGTGTGTG	CGT
rs4090473	CTTACTCCTATTCCAAAGTTCA	ACT
rs1558622	ACTGCAAGGGAGAGCCCC	ACT

dbSNP rs#	Extend Primer	Term Mix
rs1558621	AGTGTGTGTGTGTGCGTGC	ACT
rs1558620	GTCTGGTGATAGTTGGGTGC	ACG
rs1558619	GATTCCGCACATCCTATGCCT	ACT
rs950881	GATGGTTTGTGCCTCTGGTC	ACT
rs950880	ATTTAAGAATGCTTTCGTCATAAG	ACT
rs1362346	GAATATCTATGCCCACCAGAT	ACG
rs1968171	GCCCAGCATGGTGGCTCA	ACG
rs1813299	GTGGATCATGAGGTCAGGAG	CGT
rs1813298	GCCTCAGCCTCCCGAGTA	ACT
rs1968170	AGCCTGGGTGACAGAGCC	ACT
rs974389	GTCTCCTGAATTTCAGAAGCA	ACT
rs971764	GTCAAGGTAAAAACATTATTGTG	ACG
rs1420089	GCACATATCAATGACAAGACTA	ACT
rs1420088	CATGTTATGTAAGTCTGAGTTC	ACT
rs1420103	GAATATGACCTCCAGAAGGCAA	ACT
rs1420102	GAACTCAAACAAATACTTGGACAC	ACG
rs1997467	TTCAGTGAAGTCTCACAATAAGC	ACG
rs1997466	AAGAAAAAGCTGGTTCAATGAG	ACT
rs1362350	ACATTCTCTATACCAGAGATTAGG	ACT
rs2310220	CTGAAGTCAAAGTCAAGCTTTT	ACG
rs1362349	CTGTGGTACTTATCATTAAACATCA	ACT
rs3755278	ACTCGGAATTCTTTTACATTTGGT	ACT
rs3771180	CATCAAGAATTCTTAGTACATGAT	ACT
rs3771179	TATGTTAGTAAATTTCTATGTTGG	ACT
rs985523	CATATAGCTTTTACAATGATCATG	ACG
rs1041973	ATACCAGAATCAGCAACT	ACT
rs3214363	GAGCAGGGTGAAAGAAGATGGG	ACT
rs873022	TTCTAGGAATACTATCAGGTTGA	ACT
rs3771177	TTTTCACCTACTAGAGGCCC	CGT
rs3732129	GCCACATCTGTTCTTTATTCTTT	ACG
rs1420101	CCATCACAAAGCCTCTCATTA	ACT
rs12905	AGACAGCAAACAACATCC	ACG
rs3771175	CACAAAAGAACACGTTTCAGTTT	CGT
rs3821204	TAAGCATGGTCCGTTCTATAC	ACT
rs2160203	CCACACACATTATCATTGTTA	ACT
rs1946131	TTAACAACCTCTTTGGCTATTTGACA	ACT
rs1054096	TCCATCCAGCCTGCCAC	ACG
rs2287038	TACCTATGTGTTTGAATTATCTTC	ACT
rs1921622	GAAAGAGGACTTAAAAATTGATGA	ACT
rs1861246	CTTCACCTCTTCTTTTTCAGTC	ACG
rs1861245	CTGGAATGGTTTTCTACTTCC	ACG
rs3755276	GTGTGTATGCATGTGTTTCGC	ACT
rs2287037	ACAAAAGTGTGCCTATCTTATGAA	ACT
rs1420099	GGTGGGAGGTTGATAATTGAAA	ACT
rs3771174	CTGACCATCATCTACCCAGG	ACT
rs1420098	ACGTGAAGTACAAGATTCTTCA	ACT
rs1362348	GAGTAGGAAAGAAAAGGATGTG	ACT
rs1882348	TCCTATGACATGAAATACATTCT	CGT
rs1558627	AAGCAGAGAGAGATAAACTTATT	ACG

dbSNP rs#	Extend Primer	Term Mix
rs2058622	AAACCTTGGTAGCACTTCTGT	ACT
rs3836110	AACAAACACCGCCCCCCC	CGT
rs3771172	GCATTGGCCATCTTTCTGATA	ACG
rs3771171	GAGGTGTCCCAGAGTGGATA	ACG
rs3771170	CAAAGCTGCTTCTCTCCTCA	CGT
rs2160202	TATACACATATGTGTTCTAACTTA	ACT
rs2058623	ACTTAGGTGTGTAACCCTTTG	ACG
rs3771167	CTTTGTAGTTTGATGTGGGATCT	ACT
rs3771166	ACTTTACACCTGAAAATTTCCC	ACT
rs1974675	GAAGGGGATACAAAAGGGATA	ACT
rs1465321	CAGTTGGCCTCAGTGTTAACCC	ACG
rs2041740	GAACATCATGCTTTTTATGGCTG	ACG
rs3771164	GACATGTATGGAAATGTGTGTG	CGT
rs2270298	CTCTCTCTCTGCATGTGTGT	ACT
rs2270297	AGCCAAGTAGAGGAGCACC	ACT
rs2041739	CTCCTGAGTTCCTGTGAATAC	ACT
rs2080289	TCTCAGGACTCCACTCAAATGTC	ACT
rs3821203	GGCAGGAGGCAATTTCCGT	ACT
rs3771162	CAGTGAGACTCAGGAGTGC	CGT
rs3213733	TGTATCTGGTTTTCTCTCACTCA	ACT
rs3213732	CAACATTCAAAAAATGGCACTCTT	ACG
rs1035130	TCCGATCCATTTTCTTCCCC	ACT
rs3752659	CCTAGGGTATGGCCACTATAATTA	ACG
rs3755274	CACCCAACATAAAGAAAGACCTC	ACG
rs2241117	ATCATGATGCTAAGTTGAAAATAT	ACT
rs2241116	TCAAGCATTTTAAACATGTGAATT	CGT
rs881890	TGCCTTCTGGAGTCCTGTAA	ACT
rs3771161	GTGAGCACTGAAAACTTTAAGA	ACT
rs3771160	GCCAGAAAGCTGTGATTTCCTA	ACT
rs3771159	CCAACAAAGATTTGAGCCCC	ACT
rs1420104	CTGGGAGGTGGAGACTGCA	ACT
rs2041738	AAAAATACAAAAATTAGCTGGGC	ACT

Genetic Analysis

[0268] Allelotyping results from the discovery cohort are shown for cases and controls in Table 23. The allele frequency for the A2 allele is noted in the fifth and sixth columns for osteoarthritis case pools and control pools, respectively, where “AF” is allele frequency. The allele frequency for the A1 allele can be easily calculated by subtracting the A2 allele frequency from 1 (A1 AF = 1-A2 AF). For example, the SNP rs951774 has the following case and control allele frequencies: case A1 (A) = 0.24; case A2 (C) = 0.76; control A1 (A) = 0.20; and control A2 (C) = 0.80, where the nucleotide is provided in paranthesis. Some SNPs are labeled “untyped” because of failed assays.

TABLE 23

dbSNP rs#	Position in SEQ ID NO: 4	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs884517	207	102527857	C/T			
rs1476984	6019	102533669	A/G	0.83	0.83	0.973
rs951774	6414	102534064	A/C	0.76	0.80	0.099
rs2041737	7341	102534991	A/G	0.38	0.32	0.146
rs1420091	10984	102538634	A/G	0.33	0.35	0.388
rs2110660	12351	102540001	C/G	0.41	0.40	0.753
rs1362347	13335	102540985	A/G	0.83	0.83	0.895
rs3073968	16584	102544234	- /TGTG/T GTGAG	0.48	0.48	0.878
rs4090473	16737	102544387	C/G	0.42	0.43	0.633
rs1558622	23897	102551547	C/T	0.40	0.39	0.879
rs1558621	24057	102551707	C/T	0.32	0.31	0.795
rs1558620	25145	102552795	A/G	0.37	0.37	0.998
rs1558619	25300	102552950	A/C	0.46	0.47	0.556
rs950881	26262	102553912	A/C	0.75	0.74	0.636
rs950880	26312	102553962	G/T	0.45	0.48	0.285
rs1362346	26589	102554239	C/T			
rs1968171	27302	102554952	A/G	0.43	0.43	0.891
rs1813299	27358	102555008	A/T			
rs1813298	27451	102555101	C/G			
rs1968170	27552	102555202	C/T	0.65	0.65	0.941
rs974389	30731	102558381	C/T	0.41	0.42	0.734
rs971764	32085	102559735	A/G	0.45	0.44	0.738
rs1420089	32139	102559789	A/G	0.16	0.19	0.099
rs1420088	33184	102560834	A/G	0.41	0.40	0.869
rs1420103	42382	102570032	G/T	0.68	0.68	0.952
rs1420102	42569	102570219	A/G	0.48	0.46	0.349
rs1997467	44823	102572473	C/T			
rs1997466	45217	102572867	C/G	0.46	0.46	0.693
rs1362350	45548	102573198	C/G	0.48	0.46	0.475
rs2310220	45601	102573251	A/G	0.40	0.41	0.480
rs1362349	45722	102573372	C/G	0.41	0.42	0.893
rs3755278	45967	102573617	A/G	0.07	0.08	0.876
rs3771180	47367	102575017	A/C	0.91	0.90	0.669
rs3771179	47642	102575292	A/C	0.08	0.08	0.986
rs985523	48126	102575776	C/T	0.17	0.13	0.064
rs1041973	49218	102576868	A/C			
rs3214363	49274	102576924	-/A			
rs873022	49433	102577083	G/T	0.53	0.56	0.321
rs3771177	49610	102577260	A/C	0.33	0.31	0.278
rs3732129	51282	102578932	A/G	0.46	0.50	0.127
rs1420101	51466	102579116	A/G	0.55	0.57	0.257
rs12905	53757	102581407	A/G	0.30	0.27	0.262
rs3771175	53960	102581610	A/T	0.84	0.82	0.174
rs3821204	54031	102581681	C/G	0.26	0.23	0.222
rs2160203	54574	102582224	C/T	0.21	0.26	0.033
rs1946131	55679	102583329	A/G	0.73	0.74	0.710
rs1054096	56100	102583750	C/T	0.69	0.65	0.137
rs2287038	56182	102583832	C/T	0.98	0.95	0.207
rs1921622	59817	102587467	A/G	0.40	0.43	0.218
rs1861246	60533	102588183	A/G	0.22	0.18	0.068
rs1861245	60656	102588306	A/G	0.35	0.37	0.377
rs3755276	72209	102599859	A/G	0.51	0.48	0.355
rs2287037	72778	102600428	A/G	0.49	0.53	0.195
rs1420099	74293	102601943	C/G	0.58	0.56	0.416
rs3771174	77335	102604985	A/G			
rs1420098	78029	102605679	A/G	0.33	0.32	0.532
rs1362348	78374	102606024	C/G	0.02	0.03	0.590

dbSNP rs#	Position in SEQ ID NO: 4	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1882348	78421	102606071	A/T	0.36	0.35	0.596
rs1558627	78434	102606084	C/T	0.62	0.65	0.219
rs2058622	79174	102606824	C/T	0.57	0.59	0.528
rs3836110	79397	102607047	-/G	0.72	0.73	0.856
rs3771172	79562	102607212	A/G	0.28	0.25	0.261
rs3771171	79700	102607350	A/G			
rs3771170	79730	102607380	A/T	0.24	0.23	0.533
rs2160202	79904	102607554	C/T	0.55	0.62	0.061
rs2058623	79920	102607570	A/G	0.67	0.68	0.631
rs3771167	79938	102607588	C/T			
rs3771166	79972	102607622	C/T	0.55	0.53	0.624
rs1974675	80125	102607775	C/T	0.57	0.55	0.470
rs1465321	80368	102608018	A/G	0.27	0.26	0.614
rs2041740	83484	102611134	C/T	0.26	0.25	0.622
rs3771164	85536	102613186	A/T	0.76	0.73	0.197
rs2270298	85829	102613479	C/T	0.23	0.21	0.329
rs2270297	86425	102614075	A/G	0.60	0.60	0.900
rs2041739	88083	102615733	A/G	0.43	0.40	0.235
rs2080289	88770	102616420	C/T	0.56	0.59	0.322
rs3821203	90622	102618272	A/G	0.58	0.62	0.194
rs3771162	90924	102618574	A/T	0.30	0.28	0.260
rs3213733	91634	102619284	G/T	0.76	0.73	0.287
rs3213732	92029	102619679	C/T	0.44	0.42	0.507
rs1035130	95152	102622802	A/G	0.58	0.61	0.234
rs3752659	95348	102622998	C/T	0.80	0.80	0.957
rs3755274	96145	102623795	C/T	0.26	0.25	0.549
rs2241117	96793	102624443	A/G	0.71	0.75	0.077
rs2241116	97015	102624665	G/T	0.16	0.15	0.469
rs881890	97064	102624714	C/T			
rs3771161	97711	102625361	G/T	0.70	0.68	0.348
rs3771160	97855	102625505	A/C			
rs3771159	98708	102626358	A/G	0.38	0.40	0.294
rs1420104	not mapped	not mapped	C/T			
rs2041738	not mapped	not mapped	A/C			

[0269] The *IL1RL1* proximal SNPs were also allelotyped in the replication cohorts using the methods described herein and the primers provided in Tables 21 and 22. The replication allelotyping results for replication cohort #1 and replication cohort #2 are provided in Tables 24 and 25, respectively.

TABLE 24

dbSNP rs#	Position in SEQ ID NO: 4	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs884517	207	102527857	C/T			
rs1476984	6019	102533669	A/G	0.82	0.81	0.878
rs951774	6414	102534064	A/C	0.76	0.82	0.024
rs2041737	7341	102534991	A/G	0.36	0.32	0.382
rs1420091	10984	102538634	A/G	0.32	0.35	0.340
rs2110660	12351	102540001	C/G	0.39	0.39	0.951
rs1362347	13335	102540985	A/G	0.83	0.83	0.766
rs3073968	16584	102544234	- /TGTG/T GTGAG	0.47	0.48	0.822
rs4090473	16737	102544387	C/G	0.40	0.41	0.663
rs1558622	23897	102551547	C/T	0.38	0.38	0.943
rs1558621	24057	102551707	C/T	0.33	0.32	0.631
rs1558620	25145	102552795	A/G	0.34	0.34	0.957
rs1558619	25300	102552950	A/C	0.44	0.47	0.368

dbSNP rs#	Position in SEQ ID NO: 4	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs950881	26262	102553912	A/C	0.76	0.74	0.476
rs950880	26312	102553962	G/T	0.42	0.47	0.199
rs1362346	26589	102554239	C/T			
rs1968171	27302	102554952	A/G	0.43	0.44	0.641
rs1813299	27358	102555008	A/T			
rs1813298	27451	102555101	C/G			
rs1968170	27552	102555202	C/T	0.64	0.65	0.797
rs974389	30731	102555831	C/T	0.39	0.41	0.678
rs971764	32085	102559735	A/G	0.47	0.46	0.710
rs1420089	32139	102559789	A/G	0.16	0.21	0.075
rs1420088	33184	102560834	A/G	0.41	0.40	0.869
rs1420103	42382	102570032	G/T	0.69	0.72	0.268
rs1420102	42569	102570219	A/G	0.50	0.47	0.329
rs1997467	44823	102572473	C/T			
rs1997466	45217	102572867	C/G	0.49	0.47	0.675
rs1362350	45548	102573198	C/G	0.51	0.47	0.308
rs2310220	45601	102573251	A/G	0.40	0.44	0.282
rs1362349	45722	102573372	C/G	0.42	0.43	0.730
rs3755278	45967	102573617	A/G	0.08	0.08	0.902
rs3771180	47367	102575017	A/C	0.93	0.92	0.591
rs3771179	47642	102575292	A/C	0.08	0.08	0.936
rs985523	48126	102575776	C/T	0.17	0.13	0.156
rs1041973	49218	102576868	A/C			
rs3214363	49274	102576924	-A			
rs873022	49433	102577083	G/T	0.51	0.56	0.138
rs3771177	49610	102577260	A/C	0.36	0.32	0.125
rs3732129	51282	102578932	A/G	0.43	0.50	0.048
rs1420101	51466	102579116	A/G	0.50	0.55	0.132
rs12905	53757	102581407	A/G	0.33	0.28	0.127
rs3771175	53960	102581610	A/T	0.86	0.83	0.217
rs3821204	54031	102581681	C/G	0.29	0.23	0.071
rs2160203	54574	102582224	C/T	0.19	0.26	0.016
rs1946131	55679	102583329	A/G	0.72	0.73	0.771
rs1054096	56100	102583750	C/T	0.70	0.65	0.079
rs2287038	56182	102583832	C/T	0.93	NA	0.975
rs1921622	59817	102587467	A/G	0.37	0.41	0.260
rs1861246	60533	102588183	A/G	0.22	0.15	0.031
rs1861245	60656	102588306	A/G	0.34	0.39	0.149
rs3755276	72209	102599859	A/G	0.53	0.46	0.072
rs2287037	72778	102600428	A/G	0.45	0.51	0.069
rs1420099	74293	102601943	C/G	0.59	0.55	0.312
rs3771174	77335	102604985	A/G			
rs1420098	78029	102605679	A/G	0.35	0.32	0.328
rs1362348	78374	102606024	C/G	0.02	NA	0.025
rs1882348	78421	102606071	A/T	0.40	0.37	0.399
rs1558627	78434	102606084	C/T	0.64	0.69	0.118
rs2058622	79174	102606824	C/T	0.59	0.62	0.491
rs3836110	79397	102607047	-G	0.74	0.75	0.625
rs3771172	79562	102607212	A/G	0.31	0.27	0.200
rs3771171	79700	102607350	A/G			
rs3771170	79730	102607380	A/T	0.22	0.20	0.346
rs2160202	79904	102607554	C/T	0.55	0.60	0.217
rs2058623	79920	102607570	A/G	0.69	0.72	0.266
rs3771167	79938	102607588	C/T			
rs3771166	79972	102607622	C/T	0.57	untyped	NA
rs1974675	80125	102607775	C/T	0.58	0.54	0.297
rs1465321	80368	102608018	A/G	0.25	0.23	0.471
rs2041740	83484	102611134	C/T	0.25	0.22	0.450
rs3771164	85536	102613186	A/T	0.77	0.72	0.073
rs2270298	85829	102613479	C/T	0.25	0.22	0.324
rs2270297	86425	102614075	A/G	0.63	0.64	0.589
rs2041739	88083	102615733	A/G	0.44	0.40	0.157
rs2080289	88770	102616420	C/T	0.53	0.58	0.114
rs3821203	90622	102618272	A/G	0.55	0.61	0.104

dbSNP rs#	Position in SEQ ID NO: 4	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3771162	90924	102618574	A/T	0.34	0.29	0.261
rs3213733	91634	102619284	G/T	0.77	0.73	0.260
rs3213732	92029	102619679	C/T	0.48	0.41	0.026
rs1035130	95152	102622802	A/G	0.55	0.60	0.152
rs3752659	95348	102622998	C/T	0.81	0.80	0.760
rs3755274	96145	102623795	C/T	0.25	0.22	0.319
rs2241117	96793	102624443	A/G	0.72	0.80	0.024
rs2241116	97015	102624665	G/T	0.18	NA	NA
rs881890	97064	102624714	C/T			
rs3771161	97711	102625361	G/T	0.71	0.66	0.146
rs3771160	97855	102625505	A/C			
rs3771159	98708	102626358	A/G	0.38	0.42	0.175
rs1420104	not mapped	not mapped	C/T			
rs2041738	not mapped	not mapped	A/C			

TABLE 25

dbSNP rs#	Position in SEQ ID NO: 4	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs884517	207	102527857	C/T			
rs1476984	6019	102533669	A/G	0.84	0.85	0.759
rs951774	6414	102534064	A/C	0.77	0.75	0.730
rs2041737	7341	102534991	A/G	0.40	NA	
rs1420091	10984	102538634	A/G	0.34	0.35	0.819
rs2110660	12351	102540001	C/G	0.43	0.42	0.665
rs1362347	13335	102540985	A/G	0.82	0.83	0.576
rs3073968	16584	102544234	- /TGTG/T GTGAG	0.49	0.49	0.997
rs4090473	16737	102544387	C/G	0.44	0.45	0.732
rs1558622	23897	102551547	C/T	0.42	0.42	0.976
rs1558621	24057	102551707	C/T	0.31	0.31	0.926
rs1558620	25145	102552795	A/G	0.42	0.42	0.867
rs1558619	25300	102552950	A/C	0.48	0.48	0.930
rs950881	26262	102553912	A/C	0.73	0.73	0.955
rs950880	26312	102553962	G/T	0.48	0.49	0.919
rs1362346	26589	102554239	C/T			
rs1968171	27302	102554952	A/G	0.43	0.42	0.717
rs1813299	27358	102555008	A/T			
rs1813298	27451	102555101	C/G			
rs1968170	27552	102555202	C/T	0.67	0.66	0.830
rs974389	30731	102558381	C/T	0.44	0.45	0.857
rs971764	32085	102559735	A/G	0.43	0.42	0.845
rs1420089	32139	102559789	A/G	0.15	0.16	0.809
rs1420088	33184	102560834	A/G			
rs1420103	42382	102570032	G/T	0.68	0.63	0.178
rs1420102	42569	102570219	A/G	0.45	0.44	0.722
rs1997467	44823	102572473	C/T			
rs1997466	45217	102572867	C/G	0.44	0.43	0.805
rs1362350	45548	102573198	C/G	0.45	0.46	0.890
rs2310220	45601	102573251	A/G	0.38	0.37	0.661
rs1362349	45722	102573372	C/G	0.41	0.40	0.762
rs3755278	45967	102573617	A/G	0.07	0.07	0.984
rs3771180	47367	102575017	A/C	0.88	0.87	0.812
rs3771179	47642	102575292	A/C	0.07	0.07	0.868
rs985523	48126	102575776	C/T	0.16	0.13	0.270
rs1041973	49218	102576868	A/C			
rs3214363	49274	102576924	-/A			
rs873022	49433	102577083	G/T	0.57	0.56	0.868
rs3771177	49610	102577260	A/C	0.29	0.29	0.988
rs3732129	51282	102578932	A/G	0.51	0.52	0.795
rs1420101	51466	102579116	A/G	0.60	0.61	0.864
rs12905	53757	102581407	A/G	0.26	0.26	0.994

dbSNP rs#	Position in SEQ ID NO: 4	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3771175	53960	102581610	A/T	0.82	0.80	0.444
rs3821204	54031	102581681	C/G	0.22	0.23	0.769
rs2160203	54574	102582224	C/T	0.23	0.25	0.732
rs1946131	55679	102583329	A/G	0.75	0.77	0.723
rs1054096	56100	102583750	C/T	0.66	0.65	0.807
rs2287038	56182	102583832	C/T	0.97	0.00	
rs1921622	59817	102587467	A/G	0.44	0.46	0.472
rs1861246	60533	102588183	A/G	0.23	0.24	0.824
rs1861245	60656	102588306	A/G	0.36	0.34	0.590
rs3755276	72209	102599859	A/G	0.48	0.51	0.423
rs2287037	72778	102600428	A/G	0.55	0.54	0.941
rs1420099	74293	102601943	C/G	0.58	0.58	0.904
rs3771174	77335	102604985	A/G			
rs1420098	78029	102605679	A/G	0.30	0.31	0.827
rs1362348	78374	102606024	C/G	0.04	-0.01	
rs1882348	78421	102606071	A/T	0.31	0.31	0.968
rs1558627	78434	102606084	C/T	0.60	0.59	0.839
rs2058622	79174	102606824	C/T	0.56	0.55	0.961
rs3836110	79397	102607047	-G	0.70	0.69	0.643
rs3771172	79562	102607212	A/G	0.24	0.22	0.675
rs3771171	79700	102607350	A/G			
rs3771170	79730	102607380	A/T	0.26	0.27	0.700
rs2160202	79904	102607554	C/T	untyped	0.64	NA
rs2058623	79920	102607570	A/G	0.65	0.62	0.389
rs3771167	79938	102607588	C/T			
rs3771166	79972	102607622	C/T	0.53	0.53	0.820
rs1974675	80125	102607775	C/T	0.55	0.56	0.842
rs1465321	80368	102608018	A/G	0.29	0.30	0.781
rs2041740	83484	102611134	C/T	0.28	0.30	0.658
rs3771164	85536	102613186	A/T	0.73	0.74	0.905
rs2270298	85829	102613479	C/T	0.19	0.18	0.654
rs2270297	86425	102614075	A/G	0.57	0.53	0.249
rs2041739	88083	102615733	A/G	0.42	0.41	0.892
rs2080289	88770	102616420	C/T	0.61	0.60	0.840
rs3821203	90622	102618272	A/G	0.62	0.63	0.927
rs3771162	90924	102618574	A/T	0.26	0.25	0.621
rs3213733	91634	102619284	G/T	0.75	0.74	0.728
rs3213732	92029	102619679	C/T	0.39	0.45	0.176
rs1035130	95152	102622802	A/G	0.62	0.63	0.792
rs3752659	95348	102622998	C/T	0.79	0.80	0.826
rs3755274	96145	102623795	C/T	0.27	0.29	0.618
rs2241117	96793	102624443	A/G	0.70	0.67	0.480
rs2241116	97015	102624665	G/T	0.15	0.15	0.849
rs881890	97064	102624714	C/T			
rs3771161	97711	102625361	G/T	0.68	0.70	0.681
rs3771160	97855	102625505	A/C			
rs3771159	98708	102626358	A/G	0.37	0.37	0.970
rs1420104	not mapped	not mapped	C/T			
rs2041738	not mapped	not mapped	A/C			

[0270] Allelotyping results were considered particularly significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The allelotyping p-values were plotted in Figure 1C for the discovery cohort. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figure 1C can be determined by consulting Table 23. For example, the left-most X on the left graph is at

position 102527857. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0271] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The generally bottom-most curve is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0272] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is placed at the 3' end of each gene to show the direction of transcription.

Example 7

WASPIP Region Proximal SNPs

[0273] It has been discovered that rs1465621 in the untranslated region (UTR) of the *WASPIP* gene is associated with occurrence of osteoarthritis in subjects. This gene encodes a protein that plays a role in actin cytoskeleton organization. The encoded protein binds to a region of Wiskott-Aldrich syndrome protein that is frequently mutated in Wiskott-Aldrich syndrome, an X-linked recessive disorder. Impairment of the interaction between these two proteins may contribute to the disease. Alternative transcript variants exist for this gene. Biological activity of *WASPIP* or a pathway member downstream of *WASPIP* (e.g., IL-2) can be modulated by addition of an antibody, a recombinant binding partner, a binding agent, or a recombinant *WASPIP* or downstream pathway member protein or functional fragment thereof.

[0274] Sixty-one additional allelic variants proximal to rs1465621 were identified and subsequently allelotyped in osteoarthritis case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 26. The chromosome positions provided in column four of Table 26 are based on Genome "Build 34" of NCBI's GenBank.

TABLE 26

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 5	Chromosome Position	Allele Variants
rs1864455	2	209	175603909	C/T
rs1971763	2	5908	175609608	C/T
rs934269	2	7460	175611160	A/G
rs934270	2	7733	175611433	A/G
rs2033309	2	7855	175611555	A/G
rs2033310	2	7904	175611604	A/C
rs934271	2	8869	175612569	G/T
rs934272	2	9480	175613180	C/T
rs1897110	2	13820	175617520	C/T
rs2033311	2	15152	175618852	A/G
rs1010027	2	17713	175621413	A/G
rs1010028	2	17804	175621504	C/T
rs2884502	2	18220	175621920	C/T
rs1430177	2	19083	175622783	C/T
rs1430178	2	19123	175622823	C/G
rs3043779	2	19605	175623305	-/GTAAA
rs1549742	2	20247	175623947	G/T
rs3043781	2	20592	175624292	-/CCCCC
rs2033313	2	21907	175625607	C/T
rs7739	2	23273	175626973	C/T
rs11482	2	23299	175626999	A/C
rs3087907	2	23623	175627323	G/T
rs2358888	2	23669	175627369	A/T
rs1046036	2	23844	175627544	A/T
rs3205060	2	24190	175627890	A/G
rs15327	2	24486	175628186	C/T
rs1430179	2	24896	175628596	A/C
rs1430180	2	25118	175628818	C/G
rs2163236	2	30551	175634251	C/G
rs3217351	2	30844	175634544	-/GAGA
rs2303891	2	30900	175634600	A/G
rs3815969	2	30942	175634642	A/G
rs2288622	2	31699	175635399	A/G
rs2288623	2	32081	175635781	G/T
rs1044335	2	35078	175638778	A/G
rs2288624	2	36196	175639896	A/T
rs1060511	2	36541	175640241	A/C
rs1367218	2	38356	175642056	A/G
rs1367217	2	45578	175649278	A/G
rs1465621	2	49634	175653334	A/T
rs1465622	2	49774	175653474	G/T
rs2115872	2	51119	175654819	A/G
rs1465623	2	51181	175654881	A/G
rs1469521	2	51652	175655352	C/T
rs1864451	2	54467	175658167	C/G
rs1430183	2	55762	175659462	A/G
rs1430182	2	55999	175659699	A/G
rs1430181	2	57865	175661565	A/C

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 5	Chromosome Position	Allele Variants
rs1991601	2	66613	175670313	A/G
rs2358890	2	68377	175672077	C/T
rs2115875	2	69754	175673454	C/T
rs1430185	2	72859	175676559	A/G
rs2217429	2	76512	175680212	A/G
rs3049909	2	76717	175680417	-/AT
rs1430184	2	77722	175681422	C/T
rs2278321	2	80998	175684698	A/G
rs2115874	2	82033	175685733	C/T
rs2033315	2	89658	175693358	C/T
rs2033314	2	89960	175693660	A/G
rs1991600	2	94155	175697855	A/G
rs1864453	2	95679	175699379	A/G

Assay for Verifying and Allelotyping SNPs

[0275] The methods used to verify and allelotype the 61 proximal SNPs of Table 26 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 27 and Table 28, respectively.

TABLE 27

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs1864455	ACGTTGGATGACAGGTGTGCAGTGAATGTC	ACGTTG GATGTCAGCAGTTGTCCCATCTTC
rs1971763	ACGTTGGATGAATGATTTACTTGAGGCCGG	ACGTTG GATGTCTCAAACCTCTGACCTCTG
rs934269	ACGTTGGATGAAGTCCCTAGGACTACAGGT	ACGTTG GATGTGGGCAACATAGCAAGACCC
rs934270	ACGTTGGATGATGATCTGCCCTGTTCTTGC	ACGTTG GATGAGGTGCAATCTACTCACCAG
rs2033309	ACGTTGGATGCCATAGCTTCCTCACACAAC	ACGTTG GATGTTCTCCTTGCAGACAAGGTG
rs2033310	ACGTTGGATGATGAGTCTCTGTGAGTTGAG	ACGTTG GATGTTGTGTGAGGAAGCTATGGC
rs934271	ACGTTGGATGCCTGAAATGCCAAGAAGAATG	ACGTTG GATGATTCTTGCTACATAGTCAGG
rs934272	ACGTTGGATGAGTCTTGCTTCTCTTCACAC	ACGTTG GATGACTAAGAGGTATTTGGGTGC
rs1897110	ACGTTGGATGTCAGCATCCCAAAGTGCTAG	ACGTTG GATGTAAAAATCGGCTGGGTGTGG
rs2033311	ACGTTGGATGCGGGACTCTGTGTTAACAAG	ACGTTG GATGGAGTTACAAGATGCTGGAGC
rs1010027	ACGTTGGATGGCCGTCTCTGTTGTGAGAAG	ACGTTG GATGAATTCCTCTCTGACTCTTTC
rs1010028	ACGTTGGATGGTAACCTAAGGCCTCACAGC	ACGTTG GATGGACTGAAAGAGTCAGAGAGG
rs2884502	ACGTTGGATGGAAATCCCATGTCAGAATC	ACGTTG GATGTGAACAGTACAAAGGAAGGG
rs1430177	ACGTTGGATGGCCAGACCCTGTCTCAAATA	ACGTTG GATGTGAGTAGCTAGGAGTATAGG
rs1430178	ACGTTGGATGTATTTGAGACAGGGTCTGGC	ACGTTG GATGTGAGCCCTGGAATTCAGAC
rs3043779	ACGTTGGATGAGTTCCCTCAACTACTGTTTG	ACGTTG GATGCCCACATGATTTAATGGAGC
rs1549742	ACGTTGGATGTGAGACACTGTGCCTAGCTG	ACGTTG GATGGGTCCAGGTTTGTGATGTC
rs3043781	ACGTTGGATGATAATAAATAGTTAGAAGCC	ACGTTG GATGAGAAGCTAATTAAGCTCAAG
rs2033313	ACGTTGGATGAAGCCGTGCACTCACAAATC	ACGTTG GATGACCACCTACAAAGCTTCTGG
rs7739	ACGTTGGATGTGATGACACAGATAGCAAAATGTG	ACGTTG GATGTTCCCTCCTTATAGTCAAGGACC
rs11482	ACGTTGGATGAAATGTTGGCATGAAATTAATTTT	ACGTTG GATGTGTGTCTGTTTACATAGTGCATG
rs3087907	ACGTTGGATGGAACACTGAGTTTAACTAGT	ACGTTG GATGAATCAGAGCTTACATGTGTG
rs2358888	ACGTTGGATGAATCAGAGCTTACATGTGTG	ACGTTG GATGGAGGTGAATGTTAAATACTG
rs1046036	ACGTTGGATGCAAAGTTGCCATTCATCCAG	ACGTTG GATGAGGGTGTAGGTGTATTAATG
rs3205060	ACGTTGGATGAAGCCAACACTTTGCCAAGC	ACGTTG GATGTCCTCTCTCCTCTACCATTC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs15327	ACGTTGGATGGGGTTGGTTCTTGGTAGCA	ACGTTGGATGCCTAAACATTGTATCATGGTTTCA
rs1430179	ACGTTGGATGAGACTAGGAAGGCTTGGTAG	ACGTTGGATGGGTTCCCTTCTTCTCCATG
rs1430180	ACGTTGGATGCTTCAAAGTACCAAGGTCAG	ACGTTGGATGCAGGCTTTCCATTTGTTTCC
rs2163236	ACGTTGGATGTTGAGTAGCCTGAGTGACAC	ACGTTGGATGTAGATGGCTCCAAAGGGTTC
rs3217351	ACGTTGGATGGTAACGAAAGGCACAGAATG	ACGTTGGATGTAGCACTTCCAGCTTTTCTG
rs2303891	ACGTTGGATGACCACAGACATCAGTGCTAG	ACGTTGGATGCAGTGTACTAATTCGTGACC
rs3815969	ACGTTGGATGGAAGTGCTACAAAGGTCACG	ACGTTGGATGGCTGGATCCTAATCACTCTC
rs2288622	ACGTTGGATGGGCCTGGAGCAAAAAAGAC	ACGTTGGATGCATCAGCTGTACACCAATGG
rs2288623	ACGTTGGATGGAATTTATTTAGGTCTTCAG	ACGTTGGATGTATACATCACAGAAACATGC
rs1044335	ACGTTGGATGCTACTCAGTGTCTCATCTC	ACGTTGGATGTTAAGTGGCACACGACACG
rs2288624	ACGTTGGATGCATAGGCTGTAGAAGTTGGG	ACGTTGGATGTTGTTGGTCTTCTTGGGAG
rs1060511	ACGTTGGATGTCCCTATGAAGAGAAATGCC	ACGTTGGATGCTGATGGTCTTTTCCCTTTC
rs1367218	ACGTTGGATGTTGTGAGCCGCTTTTCAAAC	ACGTTGGATGCATGCAAAACACTTTTTCAG
rs1367217	ACGTTGGATGGAGCTGTAATAAAAAAGGGTG	ACGTTGGATGTTGTATATTGCCAAAGATGC
rs1465621	ACGTTGGATGTTCTCCTCCCATCTTCTCTG	ACGTTGGATGGCGGGACTAGAAGTAGATTTC
rs1465622	ACGTTGGATGGGTCTTTGAGTGCTCCAAAC	ACGTTGGATGAGAATGTCAGGTGGAAGCA
rs2115872	ACGTTGGATGTAGACCGCCACTTTGAATG	ACGTTGGATGAAGACACTGCTGGACTTGTG
rs1465623	ACGTTGGATGGGATCCAGCAGATTCTCCAT	ACGTTGGATGAGTGGGCGGTCTAGAAAATG
rs1469521	ACGTTGGATGTGGTCTAGGAGACGTCTGA	ACGTTGGATGAGGACTGGGTGCCTGTGTTA
rs1864451	ACGTTGGATGCTGTATGTGAAAACAAAAGCC	ACGTTGGATGTTCTTACTTGGTGTGTTGAC
rs1430183	ACGTTGGATGCATGTCATTCTGTAGTGTGG	ACGTTGGATGTCCTTGGATCAAGAAAAGTG
rs1430182	ACGTTGGATGAATGTTGCTAAAAGTAACCC	ACGTTGGATGATCTTTTGGGGAAAAGAAG
rs1430181	ACGTTGGATGAAGCTCCTAGCCAGTCTTAG	ACGTTGGATGTATTTTGGCGGGGAGTAGG
rs1991601	ACGTTGGATGATCCTCAACAGATCTGGTTC	ACGTTGGATGTCTGGTGATGGCTTGTGATC
rs2358890	ACGTTGGATGTCAGAGTAGAGTTACTCCAG	ACGTTGGATGCATGATGCAGCTATTCTGTG
rs2115875	ACGTTGGATGCAGACCCTTTTTTCTAGATC	ACGTTGGATGACTATTTTTGAAGTAGTGTG
rs1430185	ACGTTGGATGATCTGAGCCTAGACCTTAAC	ACGTTGGATGGGGAATGAATACAACAGTGC
rs2217429	ACGTTGGATGTGCACAAAATTAGCCACAGC	ACGTTGGATGAGTGACCGTTTCTGTGTGTT
rs3049909	ACGTTGGATGCAAAAGCAGGAATGCCTTGG	ACGTTGGATGGGGTCACAACCTGCTGTTTTC
rs1430184	ACGTTGGATGAATTAGCAATGGCTCTCTCC	ACGTTGGATGCCTAAAAACACAGTTGCTCC
rs2278321	ACGTTGGATGCAGACAGCAGGTAGATGAAC	ACGTTGGATGTCGGAAAAGAGAGACAGCC
rs2115874	ACGTTGGATGCAGTGGACTTAAGAGAGGAG	ACGTTGGATGGGTTCAGGTACCTGAAAAGC
rs2033315	ACGTTGGATGGTCAAGGTAGTTGAGAGTATT	ACGTTGGATGCAATGACAAAAAGCAATTTTC
rs2033314	ACGTTGGATGCATCTTCTTAATGGTCTTGG	ACGTTGGATGATGCAGAGTCACATTCCATG
rs1991600	ACGTTGGATGTTTCGTCATCAGTCAGAAGG	ACGTTGGATGCTGGTCTCTTTTGGGAG
rs1864453	ACGTTGGATGAGATAGGAATGACTGCCAAG	ACGTTGGATGAGGTGACTTCATCTCTTCC

TABLE 28

dbSNP rs#	Extend Primer	Term Mix
rs1864455	TCCTTTTCTCTCAGTTCCCC	ACT
rs1971763	AGCACTTTGGGAGGCCAAGG	ACG
rs934269	GCACGCCACCACACTCGG	ACG
rs934270	CCCTGTTCTTGCTCCTGCTTCTT	ACT
rs2033309	ACAACACAAAGAAGGGTTGTTA	ACG
rs2033310	GGGTGGGAAATCTGCTGAG	ACT
rs934271	GCATAATTTTTCAGGGAGGCAG	ACT
rs934272	TGCTTCTCTTCACACTTATAAG	ACG
rs1897110	GCATCCCAAAGTGCTAGGATTACA	ACT

dbSNP rs#	Extend Primer	Term Mix
rs203331 1	CTTCCAGGAGGTGCGATGAG	ACT
rs101002 7	TCTGTTGTGAGAAGATGCGC	ACT
rs101002 8	ACAGCTGTTGGGCTCACAG	ACT
rs288450 2	TGCCTAGTTAATTTGCTTTCCT	ACT
rs143017 7	CCCTGTCTCAAATAAATTTTAAAA	ACT
rs143017 8	GACAGGGTCTGGCTATGTTGTC	ACT
rs304377 9	ACTGTTTGTGATGATTGAATAA	ACT
rs154974 2	GCCTAGCTGGGGCTTCAAGTTA	CGT
rs304378 1	TAGAAGCCAACCCCCCCC	ACT
rs203331 3	CCCTGTGAGGCCATAGACAA	ACT
rs7739	CTGTTTACATAGTGCATG	ACT
rs11482	CTTATAGTCAAGGACCGT	CGT
rs308790 7	CAATATAAAATAAGAGGTGAATGT	ACT
rs235888 8	GCTTACATGTGTGTTTTTT	CGT
rs104603 6	CATTCATCCAGAATAGATTGTTTT	CGT
rs320506 0	TTTGCCAAGCTTGTTATA	ACG
rs15327	GGTAGCATCTCCAGTAA	ACG
rs143017 9	GAGGGGAAAAAAGTCAGGAAAA	ACT
rs143018 0	AAGTACCAAGGTCAGAAATTGATT	ACT
rs216323 6	AGTCCAGGCTTCTTGCCCTG	ACT
rs321735 1	AGGCACAGAATGAAAGAGAGA	ACT
rs230389 1	TAGAAGTTTACAGAAAAGCTGGAA	ACT
rs381596 9	TTAGTACACTGACATATATACAG	ACT
rs228862 2	CTTACATCCACATTCCATTACC	ACT
rs228862 3	TTTTAGGTCTTCAGAAGAACAAG	ACT
rs104433 5	GAAATATTGGTCCCCTTTCC	ACG
rs228862 4	GACTCGCAGGTAAATAGAGCT	CGT
rs106051 1	CCCCAAAAAAGTGGA	CGT
rs136721 8	CTTTTCAAACACGATGGAGCAC	ACT
rs136721 7	AACTAAAAAGGGTGATTTCATAT	ACT
rs146562 1	CCATTCTTCCTGACATTCGCC	CGT
rs146562 2	CAAACATAAGGTTGACCCCC	CGT
rs211587 2	TTTGAATGGGACTCTTCC	ACT
rs146562 3	TCCATACATGAGAGCTGCTG	ACG
rs146952 1	TAGGAGACGTCTGACTCAA	ACT
rs186445 1	GAAAAAAGCCTTTTCTGTC	ACT
rs143018 3	ATTCTGTAGTGTGGGCCCTA	ACT
rs143018 2	GTAACCCCTTAAATACTATCATAC	ACG
rs143018 1	CTAGCCAGTCTTAGTGATGTT	CGT
rs199160 1	AGCTCGCCTCAGCCTACAA	ACT
rs235889 0	GTCCAGAACACCATAATCCC	ACT
rs211587 5	TTTTTTCTAGATCAGCACTGTCA	ACT
rs143018 5	CTAGACCTTAACTCCAATTTATA	ACG
rs221742 9	AGTCCTTGGTTTATGAACATTTG	ACT
rs304990 9	TTTATGTTATGCACATGCAGAC	ACT
rs143018 4	CATAAAACCAACTTATTAATCCC	ACG
rs227832 1	GCTCACAGGCTTTGTAACATC	ACT
rs211587 4	GGGGAGATCTGCCATCTCCTGG	ACT
rs203331 5	GGTAGTTGAGAGTATTGTGAGA	ACG

dbSNP rs#	Extend Primer	Term Mix
rs2033314	GTCTTGGTTTAATATCACTCCT	ACT
rs1991600	TAAAGGGGAAAAAAGCTCTAA	ACT
rs1864453	CTGCCAAGTTGAATACTGAGTT	ACT

Genetic Analysis

[0276] Allelotyping results from the discovery cohort are shown for cases and controls in Table 29. The allele frequency for the A2 allele is noted in the fifth and sixth columns for osteoarthritis case pools and control pools, respectively, where "AF" is allele frequency. The allele frequency for the A1 allele can be easily calculated by subtracting the A2 allele frequency from 1 (A1 AF = 1-A2 AF). For example, the SNP rs1971763 has the following case and control allele frequencies: case A1 (C) = 0.456; case A2 (T) = 0.544; control A1 (C) = 0.444; and control A2 (T) = 0.556, where the nucleotide is provided in paranthesis. Some SNPs are labeled "untyped" because of failed assays.

TABLE 29

dbSNP rs#	Position in SEQ ID NO: 5	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F P- Value
rs1864455	209	175603909	C/T			
rs1971763	5908	175609608	C/T	0.544	0.556	0.630
rs934269	7460	175611160	A/G			
rs934270	7733	175611433	A/G			
rs2033309	7855	175611555	A/G	0.158	0.172	0.502
rs2033310	7904	175611604	A/C	0.428	0.423	0.845
rs934271	8869	175612569	G/T			
rs934272	9480	175613180	C/T			
rs1897110	13820	175617520	C/T			
rs2033311	15152	175618852	A/G			
rs1010027	17713	175621413	A/G			
rs1010028	17804	175621504	C/T	0.448	0.449	0.965
rs2884502	18220	175621920	C/T			
rs1430177	19083	175622783	C/T	0.051	0.309	~0.0001
rs1430178	19123	175622823	C/G			
rs3043779	19605	175623305	-/GTAAA			
rs1549742	20247	175623947	G/T			
rs3043781	20592	175624292	-/CCCCC			
rs2033313	21907	175625607	C/T			
rs7739	23273	175626973	C/T	0.057	0.042	0.371
rs11482	23299	175626999	A/C	0.934	0.935	0.958
rs3087907	23623	175627323	G/T	0.427	0.425	0.918
rs2358888	23669	175627369	A/T	0.083	0.064	0.245
rs1046036	23844	175627544	A/T			
rs3205060	24190	175627890	A/G	0.478	0.483	0.859
rs15327	24486	175628186	C/T	0.901	0.917	0.336
rs1430179	24896	175628596	A/C			
rs1430180	25118	175628818	C/G			
rs2163236	30551	175634251	C/G	0.956	0.955	0.994
rs3217351	30844	175634544	-/GAGA	0.481	0.487	0.823
rs2303891	30900	175634600	A/G	0.750	0.687	0.006
rs3815969	30942	175634642	A/G	0.232	0.239	0.771
rs2288622	31699	175635399	A/G	0.863	0.828	0.082
rs2288623	32081	175635781	G/T	0.081	0.106	0.134
rs1044335	35078	175638778	A/G	0.105	0.115	0.550
rs2288624	36196	175639896	A/T	0.901	0.871	0.117
rs1060511	36541	175640241	A/C	0.968	0.979	0.413

dbSNP rs#	Position in SEQ ID NO: 5	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1367218	38356	175642056	A/G	0.931	0.958	0.068
rs1367217	45578	175649278	A/G	0.027	0.020	0.648
rs1465621	49634	175653334	A/T			
rs1465622	49774	175653474	G/T	0.084	0.108	0.161
rs2115872	51119	175654819	A/G	0.483	0.500	0.500
rs1465623	51181	175654881	A/G			
rs1469521	51652	175655352	C/T	0.433	0.435	0.953
rs1864451	54467	175658167	C/G	0.316	0.315	0.970
rs1430183	55762	175659462	A/G	0.972	0.970	0.930
rs1430182	55999	175659699	A/G	0.711	0.691	0.366
rs1430181	57865	175661565	A/C	0.939	0.943	0.836
rs1991601	66613	175670313	A/G	0.754	0.713	0.062
rs2358890	68377	175672077	C/T	0.404	0.443	0.109
rs2115875	69754	175673454	C/T	0.633	0.620	0.613
rs1430185	72859	175676559	A/G	0.768	0.750	0.445
rs2217429	76512	175680212	A/G	0.428	0.489	0.028
rs3049909	76717	175680417	-A/T	0.161	0.200	0.064
rs1430184	77722	175681422	C/T	0.025	untyped	NA
rs2278321	80998	175684698	A/G			
rs2115874	82033	175685733	C/T	0.729	0.698	0.179
rs2033315	89658	175693358	C/T	0.649	0.663	0.542
rs2033314	89960	175693660	A/G	0.697	0.692	0.835
rs1991600	94155	175697855	A/G	0.526	0.576	0.048
rs1864453	95679	175699379	A/G	0.675	0.672	0.883

[0277] The *WASPIP* proximal SNPs were also allelotyped in the replication cohorts using the methods described herein and the primers provided in Tables 27 and 28. The replication allelotyping results for replication cohort #1 and replication cohort #2 are provided in Tables 30 and 31, respectively.

TABLE 30

dbSNP rs#	Position in SEQ ID NO: 5	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1864455	209	175603909	C/T			
rs1971763	5908	175609608	C/T	0.472	0.509	0.276
rs934269	7460	175611160	A/G			
rs934270	7733	175611433	A/G			
rs2033309	7855	175611555	A/G	0.179	0.186	0.784
rs2033310	7904	175611604	A/C	0.428	0.405	0.493
rs934271	8869	175612569	G/T			
rs934272	9480	175613180	C/T			
rs1897110	13820	175617520	C/T			
rs2033311	15152	175618852	A/G			
rs1010027	17713	175621413	A/G			
rs1010028	17804	175621504	C/T	0.447	0.465	0.579
rs2884502	18220	175621920	C/T			
rs1430177	19083	175622783	C/T	0.051	0.098	0.138
rs1430178	19123	175622823	C/G			
rs3043779	19605	175623305	- /GTAAA			
rs1549742	20247	175623947	G/T			
rs3043781	20592	175624292	- /CCCCC			
rs2033313	21907	175625607	C/T			
rs7739	23273	175626973	C/T	0.076	0.053	0.342
rs11482	23299	175626999	A/C	0.919	0.919	0.996
rs3087907	23623	175627323	G/T	0.422	0.390	0.348
rs2358888	23669	175627369	A/T	0.104	0.074	0.204
rs1046036	23844	175627544	A/T			

dbSNP rs#	Position in SEQ ID NO: 5	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3205060	24190	175627890	A/G	0.501	0.472	0.391
rs15327	24486	175628186	C/T	0.883	0.904	0.370
rs1430179	24896	175628596	A/C			
rs1430180	25118	175628818	C/G			
rs2163236	30551	175634251	C/G	0.976	untyped	0.921
rs3217351	30844	175634544	-/GAGA	0.514	0.480	0.329
rs2303891	30900	175634600	A/G	0.780	0.699	0.009
rs3815969	30942	175634642	A/G	0.183	0.213	0.426
rs2288622	31699	175635399	A/G	0.856	0.818	0.201
rs2288623	32081	175635781	G/T	0.083	0.112	0.216
rs1044335	35078	175638778	A/G	0.113	0.115	0.959
rs2288624	36196	175639896	A/T	0.908	0.872	0.215
rs1060511	36541	175640241	A/C	0.971	untyped	0.945
rs1367218	38356	175642056	A/G	0.952	0.947	0.824
rs1367217	45578	175649278	A/G	0.020	untyped	NA
rs1465621	49634	175653334	A/T			
rs1465622	49774	175653474	G/T	0.077	0.118	0.108
rs2115872	51119	175654819	A/G	0.493	0.499	0.861
rs1465623	51181	175654881	A/G			
rs1469521	51652	175655352	C/T	0.453	0.427	0.436
rs1864451	54467	175658167	C/G	0.302	0.321	0.556
rs1430183	55762	175659462	A/G	0.959	0.962	0.903
rs1430182	55999	175659699	A/G	0.727	0.678	0.114
rs1430181	57865	175661565	A/C	0.942	0.940	0.943
rs1991601	66613	175670313	A/G	0.773	0.722	0.081
rs2358890	68377	175672077	C/T	0.389	0.443	0.111
rs2115875	69754	175673454	C/T	0.639	0.601	0.267
rs1430185	72859	175676559	A/G	0.790	0.774	0.586
rs2217429	76512	175680212	A/G	0.412	0.504	0.029
rs3049909	76717	175680417	-/AT	0.144	0.193	0.079
rs1430184	77722	175681422	C/T			
rs2278321	80998	175684698	A/G			
rs2115874	82033	175685733	C/T	0.744	0.703	0.169
rs2033315	89658	175693358	C/T	0.675	0.695	0.533
rs2033314	89960	175693660	A/G	0.726	0.703	0.529
rs1991600	94155	175697855	A/G	0.467	0.566	0.005
rs1864453	95679	175699379	A/G	0.702	0.680	0.468

TABLE 31

dbSNP rs#	Position in SEQ ID NO: 3	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1864455	209	175603909	C/T			
rs1971763	5908	175609608	C/T	0.635	0.629	0.879
rs934269	7460	175611160	A/G			
rs934270	7733	175611433	A/G			
rs2033309	7855	175611555	A/G	0.131	0.149	0.576
rs2033310	7904	175611604	A/C	0.428	0.452	0.548
rs934271	8869	175612569	G/T			
rs934272	9480	175613180	C/T			
rs1897110	13820	175617520	C/T			
rs2033311	15152	175618852	A/G			
rs1010027	17713	175621413	A/G			
rs1010028	17804	175621504	C/T	0.449	0.424	0.503
rs2884502	18220	175621920	C/T			
rs1430177	19083	175622783	C/T	untyped	0.642	NA
rs1430178	19123	175622823	C/G			
rs3043779	19605	175623305	-/GTAAA			
rs1549742	20247	175623947	G/T			
rs3043781	20592	175624292	-/CCCC			
rs2033313	21907	175625607	C/T			

dbSNP rs#	Position in SEQ ID NO: 3	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs7739	23273	175626973	C/T	0.032	0.023	0.700
rs11482	23299	175626999	A/C	0.953	0.960	0.743
rs3087907	23623	175627323	G/T	0.435	0.479	0.295
rs2358888	23669	175627369	A/T	0.055	0.048	0.731
rs1046036	23844	175627544	A/T			
rs3205060	24190	175627890	A/G	0.449	0.500	0.197
rs15327	24486	175628186	C/T	0.923	0.937	0.552
rs1430179	24896	175628596	A/C			
rs1430180	25118	175628818	C/G			
rs2163236	30551	175634251	C/G	0.923	untyped	
rs3217351	30844	175634544	-/GAGA	0.439	0.496	0.125
rs2303891	30900	175634600	A/G	0.712	0.667	0.208
rs3815969	30942	175634642	A/G	0.294	0.281	0.705
rs2288622	31699	175635399	A/G	0.872	0.843	0.309
rs2288623	32081	175635781	G/T	0.078	0.096	0.444
rs1044335	35078	175638778	A/G	0.094	0.117	0.366
rs2288624	36196	175639896	A/T	0.894	0.869	0.356
rs1060511	36541	175640241	A/C			
rs1367218	38356	175642056	A/G	0.903	0.976	0.001
rs1367217	45578	175649278	A/G	0.035	0.021	0.504
rs1465621	49634	175653334	A/T			
rs1465622	49774	175653474	G/T	0.092	0.093	0.959
rs2115872	51119	175654819	A/G	0.471	0.502	0.397
rs1465623	51181	175654881	A/G			
rs1469521	51652	175655352	C/T	0.408	0.447	0.282
rs1864451	54467	175658167	C/G	0.334	0.306	0.420
rs1430183	55762	175659462	A/G			
rs1430182	55999	175659699	A/G	0.691	0.711	0.547
rs1430181	57865	175661565	A/C	0.936	0.946	0.651
rs1991601	66613	175670313	A/G	0.730	0.700	0.372
rs2358890	68377	175672077	C/T	0.423	0.444	0.566
rs2115875	69754	175673454	C/T	0.625	0.650	0.510
rs1430185	72859	175676559	A/G	0.740	0.714	0.462
rs2217429	76512	175680212	A/G	0.447	0.464	0.644
rs3049909	76717	175680417	-/AT	0.184	0.212	0.386
rs1430184	77722	175681422	C/T			
rs2278321	80998	175684698	A/G			
rs2115874	82033	175685733	C/T	0.709	0.691	0.605
rs2033315	89658	175693358	C/T	0.616	0.614	0.962
rs2033314	89960	175693660	A/G	0.660	0.674	0.679
rs1991600	94155	175697855	A/G	0.602	0.590	0.749
rs1864453	95679	175699379	A/G	0.641	0.659	0.631

[0278] Allelotyping results were considered particularly significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The allelotyping p-values were plotted in Figure 1D for the discovery cohort. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figure 1D can be determined by consulting Table 29. For example, the left-most X on the left graph is at position 175603909. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0279] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The generally bottom-most curve is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0280] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is placed at the 3' end of each gene to show the direction of transcription.

Example 8

ADAMTS2 Region Proximal SNPs

[0281] It has been discovered that SNP rs398829 in *ADAMTS2* is associated with occurrence of osteoarthritis in subjects. This gene encodes a disintegrin and metalloproteinase with thrombospondin motifs-2 (*ADAMTS2*), which is a member of the *ADAMTS* protein family. Members of the family share several distinct protein modules, including a propeptide region, a metalloproteinase domain, a disintegrin-like domain, and a thrombospondin type 1 (TS) motif. *ADAMTS2* is involved in collagens 1, 2 and 5 N-terminal processing, (type II collagen is the major form in cartilage). Mutations in this gene cause Ehlers-Danlos syndrome type VIIC, a recessively inherited connective-tissue disorder that causes loose joints and fragile skin. Mild loss of function may exacerbate physical joint damage leading to a predisposition to OA and incorrectly processed collagen can act dominantly to inhibit self assembly of fibrils. Alternative splicing of the gene generates 2 transcript variants. The short transcript encodes a protein, which has no significant procollagen N-peptidase activity.

[0282] Two hundred-nine additional allelic variants proximal to rs398829 were identified and subsequently allelotyped in osteoarthritis case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 32. The chromosome positions provided in column four of Table 32 are based on Genome "Build 34" of NCBI's GenBank.

TABLE 32

dbSNP rs#	Chromosome	Position in SEQ ID NO: 6	Chromosome Position	Allele Variants
rs2278221	5	210	178695460	c/t

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 6	Chromosome Position	Allele Variants
rs1650358	5	3608	178698858	c/g
rs1643818	5	3609	178698859	c/g
rs3733916	5	4318	178699568	c/t
rs1624933	5	5593	178700843	a/g
rs1624857	5	5629	178700879	c/t
rs1624832	5	5639	178700889	a/g
rs1624829	5	5640	178700890	c/t
rs2161171	5	8943	178704193	a/c
rs1530499	5	17968	178713218	a/g
rs888764	5	19887	178715137	a/g
rs873987	5	21034	178716284	a/g
rs4078699	5	21085	178716335	c/t
rs870311	5	21596	178716846	a/g
rs1643817	5	23379	178718629	a/c
rs1643816	5	23432	178718682	a/c
rs1650355	5	24007	178719257	a/c
rs888763	5	26121	178721371	a/g
rs1862212	5	26273	178721523	a/t
rs1110514	5	26755	178722005	a/t
rs3797600	5	27411	178722661	c/t
rs3797602	5	27710	178722960	g/t
rs3797603	5	27842	178723092	c/t
rs3776819	5	28379	178723629	c/t
rs252076	5	29603	178724853	c/t
rs252075	5	31232	178726482	c/g
rs252074	5	31504	178726754	a/g
rs252068	5	32583	178727833	c/g
rs252069	5	32794	178728044	a/g
rs194040	5	32840	178728090	c/t
rs252070	5	33044	178728294	c/t
rs3797606	5	33150	178728400	a/c
rs171667	5	33218	178728468	a/g
rs187539	5	33513	178728763	c/t
rs3836834	5	33959	178729209	- /tatcaaactaccatga aa
rs252071	5	34486	178729736	a/g
rs252072	5	36289	178731539	c/t
rs252073	5	36570	178731820	c/t
rs379589	5	38247	178733497	a/t
rs2052472	5	38477	178733727	a/c
rs2052471	5	38518	178733768	c/t
rs2052470	5	38529	178733779	c/t
rs2052469	5	38667	178733917	a/g
rs3797608	5	39781	178735031	c/t
rs3797609	5	39856	178735106	c/t
rs3822601	5	39927	178735177	c/t
rs153131	5	40506	178735756	a/g
rs751546	5	41869	178737119	c/g
rs2279979	5	42452	178737702	c/t
rs252060	5	44788	178740038	c/t
rs3797610	5	46059	178741309	a/c

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 6	Chromosome Position	Allele Variants
rs194039	5	46846	178742096	a/g
rs168773	5	47712	178742962	a/t
rs252061	5	48796	178744046	c/t
rs187537	5	49441	178744691	c/g
rs252062	5	49602	178744852	a/t
rs2431255	5	49723	178744973	a/c
rs3797612	5	50050	178745300	c/t
rs3797613	5	50171	178745421	c/t
rs614114	5	50477	178745727	c/t
rs252063	5	50818	178746068	c/t
rs252064	5	50833	178746083	c/t
rs252065	5	50881	178746131	a/g
rs450502	5	50882	178746132	a/g
rs439252	5	51386	178746636	c/t
rs252066	5	51534	178746784	c/t
rs457957	5	52317	178747567	a/g
rs3797614	5	52368	178747618	c/t
rs423552	5	52970	178748220	a/g
rs398829	5	53023	178748273	a/g
rs416646	5	53356	178748606	a/g
rs187450	5	53882	178749132	g/t
rs337807	5	54553	178749803	c/t
rs337806	5	55475	178750725	a/c
rs1396438	5	55530	178750780	a/g
rs1396437	5	55691	178750941	c/t
rs2411811	5	55848	178751098	a/c
rs2898813	5	55879	178751129	c/g
rs189256	5	56316	178751566	a/g
rs173072	5	56911	178752161	a/c
rs337805	5	57320	178752570	a/g
rs191415	5	57391	178752641	c/t
rs180045	5	57437	178752687	c/t
rs189255	5	57478	178752728	c/g
rs652766	5	57500	178752750	c/t
rs466750	5	59111	178754361	g/t
rs442406	5	59333	178754583	a/g
rs662407	5	59715	178754965	a/g
rs592971	5	59804	178755054	a/g
rs457187	5	59851	178755101	a/g
rs459490	5	59929	178755179	c/t
rs459668	5	60052	178755302	c/t
rs462646	5	60240	178755490	c/t
rs458272	5	60359	178755609	g/t
rs463455	5	60381	178755631	a/g
rs675880	5	60456	178755706	c/t
rs810617	5	60724	178755974	c/g
rs464156	5	60875	178756125	c/t
rs458083	5	60968	178756218	a/g
rs467333	5	60978	178756228	c/g
rs465381	5	60998	178756248	c/t
rs466363	5	61557	178756807	c/t
rs2457099	5	62091	178757341	c/t

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 6	Chromosome Position	Allele Variants
rs463901	5	62645	178757895	c/t
rs465621	5	62943	178758193	a/c
rs463724	5	63131	178758381	a/t
rs465242	5	63145	178758395	g/t
rs467419	5	63406	178758656	a/g
rs456135	5	63427	178758677	c/g
rs464536	5	63554	178758804	c/t
rs461898	5	63661	178758911	a/g
rs389558	5	64093	178759343	a/g
rs466752	5	64153	178759403	c/t
rs455655	5	64409	178759659	c/g
rs463435	5	64544	178759794	c/t
rs2174971	5	65257	178760507	c/t
rs1979979	5	65626	178760876	a/g
rs411804	5	65739	178760989	a/g
rs1623885	5	66392	178761642	c/t
rs1643811	5	66720	178761970	c/t
rs434430	5	69177	178764427	a/t
rs187538	5	69336	178764586	g/t
rs252067	5	69636	178764886	a/g
rs459319	5	69823	178765073	a/g
rs467289	5	69928	178765178	c/t
rs462644	5	70547	178765797	c/t
rs458752	5	70633	178765883	c/t
rs708320	5	71805	178767055	a/c
rs457954	5	72181	178767431	c/g
rs2411810	5	72200	178767450	c/t
rs3084687	5	72474	178767724	-/at
rs69638	5	72567	178767817	c/g
rs455452	5	72973	178768223	a/g
rs464850	5	73468	178768718	a/g
rs431472	5	73889	178769139	a/g
rs2411809	5	75730	178770980	c/t
rs2457094	5	75970	178771220	a/g
rs2457095	5	76114	178771364	a/g
rs2261740	5	76342	178771592	c/t
rs1109180	5	76449	178771699	a/g
rs1109179	5	76465	178771715	c/t
rs1109178	5	76791	178772041	a/c
rs456909	5	78042	178773292	a/g
rs469124	5	80758	178776008	a/g
rs468039	5	80778	178776028	c/t
rs467017	5	81356	178776606	a/c
rs469290	5	81576	178776826	a/g
rs469090	5	81689	178776939	c/t
rs469568	5	81759	178777009	g/t
rs468386	5	81950	178777200	c/g
rs469349	5	82562	178777812	a/c
rs469099	5	83591	178778841	c/t
rs456868	5	83700	178778950	a/g
rs465389	5	83821	178779071	c/g
rs463892	5	83842	178779092	c/g

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 6	Chromosome Position	Allele Variants
rs468548	5	83923	178779173	g/t
rs654612	5	83929	178779179	a/c
rs468542	5	84021	178779271	c/g
rs469262	5	84175	178779425	c/t
rs708323	5	84417	178779667	a/g
rs469089	5	84747	178779997	c/g
rs469396	5	85746	178780996	c/g
rs468723	5	86129	178781379	c/t
rs467604	5	86335	178781585	a/g
rs338874	5	87315	178782565	c/g
rs338875	5	87648	178782898	a/g
rs1385803	5	87764	178783014	a/c
rs1385804	5	87770	178783020	c/g
rs338876	5	88221	178783471	c/t
rs189803	5	90474	178785724	a/c
rs452215	5	91148	178786398	g/t
rs641170	5	91150	178786400	g/t
rs584398	5	91160	178786410	g/t
rs385330	5	91733	178786983	c/t
rs429538	5	91772	178787022	a/c
rs371229	5	91785	178787035	c/t
rs460874	5	93140	178788390	a/t
rs646121	5	93148	178788398	a/t
rs468262	5	96080	178791330	a/g
rs467863	5	96157	178791407	c/g
rs191434	5	96313	178791563	a/c
rs2054782	5	96759	178792009	c/t
rs468499	5	97026	178792276	a/c
rs180287	5	97320	178792570	c/g
rs338877	5	97732	178792982	a/t
rs650665	5	98713	178793963	c/g
rs193419	5	99707	178794957	a/c
rs180288	5	99959	178795209	c/g
rs186834	5	100009	178795259	a/g
rs189266	5	100020	178795270	c/g
rs189267	5	100065	178795315	a/c
rs170937	5	100086	178795336	c/g
rs463263	5	101270	178796520	c/g
rs463262	5	101276	178796526	g/t
rs460454	5	101371	178796621	c/t
rs460455	5	101376	178796626	c/g
rs460505	5	101439	178796689	c/t
rs931316	5	101820	178797070	c/t
rs463431	5	102392	178797642	c/g
rs461542	5	102602	178797852	a/g
rs463557	5	102604	178797854	a/c
rs191453	5	102896	178798146	c/t
rs2271212	5	189104	178884354	c/t
rs462009	5	189134	178884384	c/t
rs2271211	5	189205	178884455	a/g
rs396474	5	Not mapped	Not mapped	a/c
rs428901	5	Not mapped	Not mapped	a/t

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 6	Chromosome Position	Allele Variants
rs452300	5	Not mapped	Not mapped	g/t
rs670256	5	Not mapped	Not mapped	g/t

Assay for Verifying and Allelotyping SNPs

[0283] The methods used to verify and allelotype the 209 proximal SNPs of Table 32 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 33 and Table 34, respectively.

TABLE 33

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs2278221	ACGTTGGATGTCTCATGGGCCACCACAAAC	ACGTTGGATGTATGCTCCTGTCAACGGGCAT
rs1650358	ACGTTGGATGTGGATGGCTCCATGTTCTTG	ACGTTGGATGAAGTGCTGGGATTACAGGTG
rs1643818	ACGTTGGATGCTGGGATTACAGGTGTGAAC	ACGTTGGATGTGGATGGCTCCATGTTCTTG
rs3733916	ACGTTGGATGCCGAGCAGGCTGTAGTGTTG	ACGTTGGATGCTTTGTACCACCTGGAACAG
rs1624933	ACGTTGGATGAGGCTGGTCTCAAACCTCCTG	ACGTTGGATGTACAAAAAGTTGGCCGTGC
rs1624857	ACGTTGGATGTGAGGTCAGGAGTTTGAGAC	ACGTTGGATGGCCACCAAGCCAGACTAAGT
rs1624832	ACGTTGGATGTGAGGTCAGGAGTTTGAGAC	ACGTTGGATGGCCACCAAGCCAGACTAAGT
rs1624829	ACGTTGGATGTGAGGTCAGGAGTTTGAGAC	ACGTTGGATGGCCACCAAGCCAGACTAAGT
rs2161171	ACGTTGGATGCCCGTCACCACTTTATTTCC	ACGTTGGATGAGAGTGGATCCAGTCTGCAG
rs1530499	ACGTTGGATGACTCCAAGATTTCCCATTTTC	ACGTTGGATGTTCTGTGTTCCACCCTATGG
rs888764	ACGTTGGATGTAGTTGAATGTTGTATTGGC	ACGTTGGATGACCGTGATAAACACAGAATG
rs873987	ACGTTGGATGGCTGTTAATCATGTGTCTGGG	ACGTTGGATGATTTGGCCACATCACCAGAC
rs4078699	ACGTTGGATGGTACCGTGGATTCTTTTAGG	ACGTTGGATGGTATTGGAAAAGAGCAGAGAC
rs870311	ACGTTGGATGTCAGGGCTCCAGTGTTGAAG	ACGTTGGATGAAAAGGAGGAGTGCCCTGTG
rs1643817	ACGTTGGATGATGGGAAACTCCTGGTCTCTG	ACGTTGGATGAAAATGCAAGCCGCCACCTG
rs1643816	ACGTTGGATGTTTTCTCCCCTTTCTAGCCC	ACGTTGGATGTTGGCATGAGAGATGGACAG
rs1650355	ACGTTGGATGTCAACAGCAACAAAACCAAA	ACGTTGGATGTTAAATAGGTCAGAGGGTTG
rs888763	ACGTTGGATGAAGAGGAAGAGACATACCAG	ACGTTGGATGAACAACATGGACTCAGGCTG
rs1862212	ACGTTGGATGGGCCACATTTTAAACAAGGG	ACGTTGGATGTCCCCTGAGGTTCCCTATAAG
rs1110514	ACGTTGGATGTGCCACGTTCCATGTTTCAG	ACGTTGGATGATCACTGTAGCCCCTTCCTG
rs3797600	ACGTTGGATGCCTTCCTGTACCTCCTTTG	ACGTTGGATGGGAAGTGACTGCTGAGCTG
rs3797602	ACGTTGGATGAGAAACAGGGACTGGCTGTGT	ACGTTGGATGAGCAGGCTCCGGGAAGTATG
rs3797603	ACGTTGGATGCACCCATCCATCATGATGTC	ACGTTGGATGTGCTACCTCAAAACAGTGGG
rs3776819	ACGTTGGATGCAAGCACCATTCATTGCAC	ACGTTGGATGAATGAGGATTGCAGTCCCC
rs252076	ACGTTGGATGACTTCTGACTTCAGGTGATC	ACGTTGGATGTATAGGAACGAAAGAAAGCC
rs252075	ACGTTGGATGTGGGAGCATTTCAGGCATG	ACGTTGGATGAAGCCTCAGATGGTTCCGAG
rs252074	ACGTTGGATGTTGCGATGGCCTCCTGGCT	ACGTTGGATGAAGTTGAGGGCTCCGGAGCA
rs252068	ACGTTGGATGGGGTAGGAAGGGTTTAAGC	ACGTTGGATGGCAGCCCCTCAATTCTTTAG
rs252069	ACGTTGGATGTGCCCATTTCTGTTATTCC	ACGTTGGATGTTTGGACTTGCCGTGCAACT
rs194040	ACGTTGGATGTGCCCATTTCTGTTATTCC	ACGTTGGATGTTTGGACTTGCCGTGCAACT
rs252070	ACGTTGGATGCTCAAGGACATTGTCCCTGG	ACGTTGGATGGGAGAAGCAGCTCTCCTTTC
rs3797606	ACGTTGGATGGTTTCCCCAAACAAGAGAGC	ACGTTGGATGGGAAATGTTCAAAGCCGCAG
rs171667	ACGTTGGATGGGGAAACACATTGTAATGCG	ACGTTGGATGCCCTTCCTCATTGTCTATTCC
rs187539	ACGTTGGATGAGCCACCCCAACCTTCAGGA	ACGTTGGATGTGCTCCTGGACATGGTTTT
rs3836834	ACGTTGGATGAAGAAACGTGACTCTTGCTC	ACGTTGGATGTAGTAATTCTGATCCTGGCC
rs252071	ACGTTGGATGGCTTCAACCTGAAACAACCC	ACGTTGGATGGGGATATTCCTCACTCTGAG
rs252072	ACGTTGGATGTTGTTTCCCCAAAGGCGACG	ACGTTGGATGTGTGTTTTCCAGAGCTGGAG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs252073	ACGTTGGATGGGGAAAGGCCGAGAAAAGTC	ACGTTGGATGACAAGCTCAGCAGAGTTCCA
rs379589	ACGTTGGATGAAACACGGGAGTACTGAGCA	ACGTTGGATGTTGTTAGCTGTCTGTCCGTC
rs2052472	ACGTTGGATGAACCAGCTCAAGGATCACCC	ACGTTGGATGAAAGGAGACGGTCAGCTGTC
rs2052471	ACGTTGGATGACAGCTGACCGTCTCCTTTG	ACGTTGGATGCCCCGTCTGGACAAGCTTTT
rs2052470	ACGTTGGATGACAGCTGACCGTCTCCTTTG	ACGTTGGATGCCCCGTCTGGACAAGCTTTT
rs2052469	ACGTTGGATGAGGGAAAGATATCGCACGCG	ACGTTGGATGAGTGAACAACCTGC TCGCCTC
rs3797608	ACGTTGGATGTGCTTTGCCTTGGCTTCTGC	ACGTTGGATGTGCACTAAGGGAGTGAGTGG
rs3797609	ACGTTGGATGTGCAGAAAGCCAAGGCAAAGC	ACGTTGGATGACAGCATTGAG TCCCCTG
rs3822601	ACGTTGGATGAGGTCAGTGAGGCCTGAGAT	ACGTTGGATGTGTCTGGCCTGAA GATCGAG
rs153131	ACGTTGGATGTAATCACGTGCTCTGATCCC	ACGTTGGATGAGCTGTCTCAGT CATGTTT
rs751546	ACGTTGGATGTCCTGCTCTGCCGTTCTACA	ACGTTGGATGATCAGCTCAAAGG ACCGGTG
rs2279979	ACGTTGGATGTATTGCTACCAGGAACACGTA	ACGTTGGATGAAAAAGGGGCCACTTCAGGG
rs252060	ACGTTGGATGTGGCCAGAGCCCGTGTTC	ACGTTGGATGCGGCCAATCCCATCTCTATG
rs3797610	ACGTTGGATGAAAAGCTTCTCCCTTGGGTG	ACGTTGGATGCAAGTAGGGCAGAAACTCAG
rs194039	ACGTTGGATGAAAGTGCTGGGATTACAGGC	ACGTTGGATGTGCTGGGAGAAGACATTAC
rs168773	ACGTTGGATGTGGTGCCTGAGATATCAC	ACGTTGGATGGATCCCTATCCTA CCTCTTC
rs252061	ACGTTGGATGTGTCACACTCCTCTTGTAAAG	ACGTTGGATGCTGTCTCTCCATGCTTTTGC
rs187537	ACGTTGGATGCGAGGATGTCATGCTAAGTG	ACGTTGGATGGTACCTCGCATAA GTGGATC
rs252062	ACGTTGGATGAAGCACATTCATGTGGCTGG	ACGTTGGATGCTGAAACTCAATG GGCACAG
rs2431255	ACGTTGGATGGGTGAAGACGGTGACTTATG	ACGTTGGATGCTGGTGTCTTGA AGAACTG
rs3797612	ACGTTGGATGAGTGAGGACGCAGGGCATTG	ACGTTGGATGAGCGTGGGCGAGCGGAGATAA
rs3797613	ACGTTGGATGATCAGAGGCAGAGACCCCCC	ACGTTGGATGGGGTGTCTGCAAGGGCGG
rs614114	ACGTTGGATGGGTTGGAGGATGTCTAGAAC	ACGTTGGATGGGCTGGATCACTA GGGTTTG
rs252063	ACGTTGGATGTTGGAATTACAGTCCGATGG	ACGTTGGATGCTGAGAGACTGAA AAGCACA
rs252064	ACGTTGGATGCTGAGAGACTGAAAAGCACA	ACGTTGGATGTTGGAATTACAGT CCGATGG
rs252065	ACGTTGGATGAAAACCTAAGGCTCAGAGGAC	ACGTTGGATGTGGGCTTGGAA TTACAGTCC
rs450502	ACGTTGGATGATGAGAAAACCAAGGCTCAG	ACGTTGGATGCTGGGCTTGGAA TTACAGTCC
rs439252	ACGTTGGATGATCTCCTGACCTCGTGATCC	ACGTTGGATGTCATAATAACGGC CGGGTGC
rs252066	ACGTTGGATGTTTCCTCTTGACCGGTCTTG	ACGTTGGATGTAAACGAATTCTGCCGATG
rs457957	ACGTTGGATGTTACGTGCATTAGAGCGAG	ACGTTGGATGAATTCCTCCCAATTCTCTC
rs3797614	ACGTTGGATGACTGCGAGCTTTAAGGAGGG	ACGTTGGATGCCAAACAGAAGC CCCTTTTC
rs423552	ACGTTGGATGGCAGGACCTCGATGTTGTAG	ACGTTGGATGATCCTAGAGGAGC ACGCCAAC
rs398829	ACGTTGGATGTAGTCATCGTCCGCAGCATG	ACGTTGGATGAAGACGGTGTCTCTCTCTTG
rs416646	ACGTTGGATGGCTGGGTCTCTCACAGTCTC	ACGTTGGATGAGACAGGCACCTC TGTGACTT
rs187450	ACGTTGGATGAGAAGGCAGGGACGATATCC	ACGTTGGATGACCAAGATGAAC CCTCTGT
rs337807	ACGTTGGATGTCACCCAGTGCTGACAGCAG	ACGTTGGATGATGCTGGGATGCCATGGGTC
rs337806	ACGTTGGATGAATTAAGAGATGGGGCCACC	ACGTTGGATGGCCCTGTGTGTT TGTCTCC
rs1396438	ACGTTGGATGTACCTTCTGGTGCCAGAATG	ACGTTGGATGCCTGGAGACAAA ACACACAG
rs1396437	ACGTTGGATGTAAAACTCTGCCTGCTCGG	ACGTTGGATGTCCAGACATTCCC CGTAGGA
rs2411811	ACGTTGGATGGAGGGATGCTCTAGAACATA	ACGTTGGATGCTGAATTTACCT GAAATGG
rs2898813	ACGTTGGATGTCCTCACCCACTTTGCCTTT	ACGTTGGATGATCGTGATAATTT TGGGGTG
rs189256	ACGTTGGATGCTCCCTATAGCAAGGCTCTA	ACGTTGGATGTTAACCAGGCC ATGAAGAG
rs173072	ACGTTGGATGAGCTGGAGATCTCTTGCTC	ACGTTGGATGCTAAACAGGAT GGTCTGG
rs337805	ACGTTGGATGGAAACAAACCAAGGAGCAGG	ACGTTGGATGATGTGGACAACG TTGGACTC
rs191415	ACGTTGGATGAATTACATGACTCGGACAAG	ACGTTGGATGTGCTGGTGAAGT ACAGAAGG
rs180045	ACGTTGGATGGTCCCAGGTTTTCTGTTCTC	ACGTTGGATGTGTACTTCACCA GCACTGAG
rs189255	ACGTTGGATGAGGTTGCAGACTCAGTCCCA	ACGTTGGATGGGGTGATTGCG GGAATGAG
rs652766	ACGTTGGATGGGGTGATTTGCGGGAATGAG	ACGTTGGATGACCATCCACGA TGCTCCC
rs466750	ACGTTGGATGTATCTCCTTAAATGCCTTGG	ACGTTGGATGTGACCAGGAGGA GTTAAAC
rs442406	ACGTTGGATGTGACAAGGTCACGTGTTCTG	ACGTTGGATGCCAGACAAGTCT GATACAGC
rs662407	ACGTTGGATGCCACAGTCACCATTAAGTGA	ACGTTGGATGCTTGAGCCATGAGT GGAATG
rs592971	ACGTTGGATGGGAAGCATTTCTTTGACTGC	ACGTTGGATGATTCCATCTCAT GGTCAAG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs457187	ACGTTGGATGTGTGAGATGAGGAGTATCTG	ACGTTGGATGGCAGTCAAAGAAATGCTTCC
rs459490	ACGTTGGATGACAGATACTCCTCATCTCAC	ACGTTGGATGGGGAGTTTTGCTGTTATAGC
rs459668	ACGTTGGATGGCTTCATTTACTGAGGTCTTC	ACGTTGGATGTGAATGTTCAACGACTACAC
rs462646	ACGTTGGATGCAATTATTCGACGGAGATTA	ACGTTGGATGCTCCTCCAAATGAATCAAGAA
rs458272	ACGTTGGATGATGCCTCCTCATTGTCATTG	ACGTTGGATGCCCAACAAAGTGATTCCAAC
rs463455	ACGTTGGATGATGCCTCCTCATTGTCATTG	ACGTTGGATGCCCAACAAAGTGATTCCAAC
rs675880	ACGTTGGATGCAGCTCCATTGATCTGTTTC	ACGTTGGATGAAGAATGACAATGAGGAGGC
rs810617	ACGTTGGATGTGATCTCAGCTTACCACAGC	ACGTTGGATGATGCCTGTAATCCCAGCTAC
rs464156	ACGTTGGATGCAGATCCAAGAATATGTGGG	ACGTTGGATGTTCTAGAAAGGAGCCAAATC
rs458083	ACGTTGGATGTGTTGTTTCTTCCCCTCCTG	ACGTTGGATGTGGCTCCTTTCTAGAATCCC
rs467333	ACGTTGGATGCTTGTTATTTCTTCCCCTCC	ACGTTGGATGTTGGCTCCTTTCTAGAATCC
rs465381	ACGTTGGATGACTTGCCCATCTGTTTCCAG	ACGTTGGATGACAAGCCTCTAAGGATAGGG
rs466363	ACGTTGGATGAAGTGACCCTGAGGTGATGG	ACGTTGGATGTGAAGACAGTTCACCCCGTG
rs2457099	ACGTTGGATGTCTCCTTACACTGCCAGCGT	ACGTTGGATGCACTGTATTGCTACTTGAGC
rs463901	ACGTTGGATGAGAGTGCCAAGTGCAAAAGG	ACGTTGGATGTGTCTTGCGTCTGTGTATCC
rs465621	ACGTTGGATGGGAAGTCATGGAAGTGCTAG	ACGTTGGATGAAAGAGCCCTAGGCTTGAA
rs463724	ACGTTGGATGAGTGTGCCTGTCTGCCCTCA	ACGTTGGATGAAGGGCAGATGGCACACTTG
rs465242	ACGTTGGATGAGTGTGCCTGTCTGCCCTCA	ACGTTGGATGAAGGGCAGATGGCACACTTG
rs467419	ACGTTGGATGAGTCCCCAAAACGTAAGTCC	ACGTTGGATGAGTCTAATTCCCTGAGCCTC
rs456135	ACGTTGGATGAGTCTAATTCCCTGAGCCTC	ACGTTGGATGACGTAAGTCCCTAATGACCGC
rs464536	ACGTTGGATGTGCTCCAGGCTTTGGTCTCT	ACGTTGGATGAATTAGACTAAGGCCATGATG
rs461898	ACGTTGGATGGGGAATACACAGCCACAGAG	ACGTTGGATGAGGTCAACGGGAACAAGGTC
rs389558	ACGTTGGATGGCAGTCTGACAGTTCTCTA	ACGTTGGATGTTTTTCTCCCTGAAGCATGG
rs466752	ACGTTGGATGGGCCTTCTCTCCTTTAGTGC	ACGTTGGATGAGTCTGACAGTTCTCTAAA
rs455655	ACGTTGGATGCTATTTGCACCCCATATGGC	ACGTTGGATGAACACACAGCATCAGGTTCC
rs463435	ACGTTGGATGTTGAGCCATAGCTGGATTG	ACGTTGGATGCTCTGCTGGGAAAATGTGAC
rs2174971	ACGTTGGATGAACACAACCTTCCCCTTCGTC	ACGTTGGATGTGAATCCTTGAGAGTGAGTG
rs1979979	ACGTTGGATGTGGCTGTGAGCACCCTACTT	ACGTTGGATGCCCAAAGGAAGGGAGAATTC
rs411804	ACGTTGGATGCAGATGACAGGCGGAAAATC	ACGTTGGATGAGGCTTCCAGATGATGTCCA
rs1623885	ACGTTGGATGAATCAGCTAGGAAGAGCCTG	ACGTTGGATGTTTCTGACCCCTCTAGGTCAG
rs1643811	ACGTTGGATGCAGGGCCCTGGTACTTTTCA	ACGTTGGATGCATGGTGGTGATTGCACCTG
rs434430	ACGTTGGATGTCCAGGAGTTCACTGTAGAG	ACGTTGGATGCACATGCATACATTATCAC
rs187538	ACGTTGGATGACATGGGGCTTGGCAAATG	ACGTTGGATGCACCTGCTCAGAAGTAGCAT
rs252067	ACGTTGGATGAGAATTGCTGTGGTGTGAGG	ACGTTGGATGTTTTTCTTGGGAGCTGTCGC
rs459319	ACGTTGGATGCCATCTCTCTGACCTAGACA	ACGTTGGATGGCTCCAAGGAAAATTGGGAG
rs467289	ACGTTGGATGGGCCCTCTTGGCTTGTCTTT	ACGTTGGATGAGGCAGTGTGCCCTCTCATC
rs462644	ACGTTGGATGATGATGTGGGTGAGCCCTTG	ACGTTGGATGTAACACTCAGCACGCACCAG
rs458752	ACGTTGGATGCACCCACATCATGTGCGCTT	ACGTTGGATGCCCTTCTCTACCCAGCACTT
rs708320	ACGTTGGATGAAACCAGCCTGGCTAACATG	ACGTTGGATGACAGGTGCCTGCTATCATAC
rs457954	ACGTTGGATGAACCAGACCTTGACTGATGG	ACGTTGGATGCCTCATACAAGTAGCCAAGG
rs2411810	ACGTTGGATGGCTTAACCAGACCTTGACTG	ACGTTGGATGAGTGTAAAGGATATCCACGGC
rs3084687	ACGTTGGATGATCCCTTGAGCCAGAGATTC	ACGTTGGATGATGTCCTGTGCACACACAAG
rs69638	ACGTTGGATGTGCTCATTGCTGTCCTCATC	ACGTTGGATGAGAAGAAAGGTGTGCAGTGG
rs455452	ACGTTGGATGAGTGATGATGAGCCTGCTGG	ACGTTGGATGTCAGGTTCCCTCTCTGTGTC
rs464850	ACGTTGGATGTCTCTCTGTGCTCCAGACCA	ACGTTGGATGTGGGCTGAGATTTCTGTGGG
rs431472	ACGTTGGATGAACCAGTGTGGGTGTGAAGC	ACGTTGGATGAGAGACTGCATCAGGCAGGA
rs2411809	ACGTTGGATGAGCGCATAAGTGACCACCAG	ACGTTGGATGGCACTCACAGGGCATTGATG
rs2457094	ACGTTGGATGTTACTGTACCTTGGGTCTC	ACGTTGGATGGGAAGTCTGTATAGACGCAG
rs2457095	ACGTTGGATGTTATCAAGGCCTGCGCAGTG	ACGTTGGATGACTCCTGACCTCAGGCAATC
rs2261740	ACGTTGGATGATCGTGCCACTGCACTCCAG	ACGTTGGATGTCATCTTTTGGTAGCCCCC
rs1109180	ACGTTGGATGCCAGGCCTGTATTGCACATC	ACGTTGGATGAGAATGCGTGTGCATGTGGG
rs1109179	ACGTTGGATGTGTAATGGTATGCAGACCCC	ACGTTGGATGGAGTGCCGTATTTGTCTTC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs1109178	ACGTTGGATGGCAAACAACAACAGCAACAG	ACGTTGGATGAAGTGTGGATTTGTGCAGAC
rs456909	ACGTTGGATGTAGCTGCTTCATCTGTAAAG	ACGTTGGATGGGCACTTTACCGATCTACTC
rs469124	ACGTTGGATGACTTGGACACACATAGGCTG	ACGTTGGATGTGAAATGCTCAGGGTGTGTG
rs468039	ACGTTGGATGTGAAATGCTCAGGGTGTGTG	ACGTTGGATGAGGACTTGGACACACATAGG
rs467017	ACGTTGGATGGTCTAGCTGCCACTAAACAG	ACGTTGGATGATGTGCCAAGAGGCTTTGAG
rs469290	ACGTTGGATGTGCCCTTTGTGTGCTCAGAG	ACGTTGGATGTCCCTCTGTGCTGTGTTGG
rs469090	ACGTTGGATGACTTGTCTTCAGGTGCTTGG	ACGTTGGATGGATGGTTAGTCTCCTGGTTC
rs469568	ACGTTGGATGAGCACCTCTGGCTTTTCATTG	ACGTTGGATGATTCACCAGGAAATCCCAAC
rs468386	ACGTTGGATGTAATCCCAGCCCTTTGGAAG	ACGTTGGATGTATGGAGACAGGGTTTTACC
rs469349	ACGTTGGATGTTAGAGACAGAGTCTCACTC	ACGTTGGATGTTGATCCCAGGAGTTCAAGG
rs469099	ACGTTGGATGTTGGAGCTGCTCTAGTTCTC	ACGTTGGATGTGAAAACCGGGACTCAGCTC
rs456868	ACGTTGGATGACAGAGCAGGGAGCTGCGGT	ACGTTGGATGATTCACCCCAGCTACTGTG
rs465389	ACGTTGGATGAGGCTTTGTAGACAGCTCCC	ACGTTGGATGTGCCAGTGCTCTGAGTATGC
rs463892	ACGTTGGATGAGGCTTTGTAGACAGCTCCC	ACGTTGGATGTGCCAGTGCTCTGAGTATGC
rs468548	ACGTTGGATGACTGGAAGGGAACATGCAAG	ACGTTGGATGCCTGGATGCCCTTTATAGAC
rs654612	ACGTTGGATGACTGGAAGGGAACATGCAAG	ACGTTGGATGTGGATGCCCTTTCTAGACAC
rs468542	ACGTTGGATGGCCTCCATTTTCCTTCTCAC	ACGTTGGATGTGTCTAGAAAGGGCATCCAG
rs469262	ACGTTGGATGTTCTGAGCTGAACGAAGCAG	ACGTTGGATGGGTCAGGGATCCTTTGATGC
rs708323	ACGTTGGATGCACATACTATACAGGTCACC	ACGTTGGATGGAGGGAGAAGATGTTGTGAA
rs469089	ACGTTGGATGTTTGGAAAGTACCACCTCAGC	ACGTTGGATGAATGGAAGGAAGGATCAGCC
rs469396	ACGTTGGATGAGTGACTCCAATGAGGGAAC	ACGTTGGATGTCTCACACCACTGATCCTTC
rs468723	ACGTTGGATGTGTGGATCTTGCTGTTTGGG	ACGTTGGATGTATTGGCATCGCGTATCAGG
rs467604	ACGTTGGATGACTCCTGCCATTAACTCTC	ACGTTGGATGCTTGGCTTAACCTACAAGGG
rs338874	ACGTTGGATGCCCCACCACAGCCACTGGG	ACGTTGGATGAAGGGCCTTGCCCCACCCAA
rs338875	ACGTTGGATGTGCTGTCTTGCTCGCGTGTG	ACGTTGGATGACACTGGATATGTCAGGGTC
rs1385803	ACGTTGGATGTCACCACCATTCCAGAAGTG	ACGTTGGATGACCTTCCTTATTGCTGTGGC
rs1385804	ACGTTGGATGTCACCACCATTCCAGAAGTG	ACGTTGGATGACCTTCCTTATTGCTGTGGC
rs338876	ACGTTGGATGTTAGGGCTGGGTGGAGGAAG	ACGTTGGATGTCCAACCTCCAGTGACAGAG
rs189803	ACGTTGGATGCCTCCAGTTTCTCTCTTCTG	ACGTTGGATGATCCTGGATTAGCCAGATGG
rs452215	ACGTTGGATGTAGCTCTATTCTTCCACCCC	ACGTTGGATGAGCGAGACTCCGTCTCAAAA
rs641170	ACGTTGGATGATAGCTCTATTCTTCCACCC	ACGTTGGATGAGCGAGACTCCGTCTCAAAA
rs584398	ACGTTGGATGTTCTGTGAGCTATAGAAAC	ACGTTGGATGCGAGACTCCGTCTCAAAAAAA
rs385330	ACGTTGGATGTTGCCCAACTATTGTCTCTG	ACGTTGGATGGGTTTCCCAGACAGTGTGTTG
rs429538	ACGTTGGATGTATTATCTGCAGACACCTGG	ACGTTGGATGATCTCATTCCCACCCTCTTC
rs371229	ACGTTGGATGTATTATCTGCAGACACCTGG	ACGTTGGATGATCTCATTCCCACCCTCTTC
rs460874	ACGTTGGATGGTCCTGCGGCTAAAAATTCC	ACGTTGGATGGGGCAGGTCAACTAGAAAAC
rs646121	ACGTTGGATGGGGCAGGTCAACTAGAAAAC	ACGTTGGATGGTCCTGCGGCTAAAAATTCC
rs468262	ACGTTGGATGGCCAGGTTTCGAAAGTTAGG	ACGTTGGATGTGGGTTGGTCATGCGGTAAC
rs467863	ACGTTGGATGTTTCGAAACCTGGCTGATGG	ACGTTGGATGTGCCACTGTCAGAAGACAAG
rs191434	ACGTTGGATGCCAGCTGAAACACTAGACAG	ACGTTGGATGAGCTGAAGAGGTCTTTCTCC
rs2054782	ACGTTGGATGAAAAAAGCAGGCCTCAGACC	ACGTTGGATGTCTGACTCTCATCTGCAGAC
rs468499	ACGTTGGATGCTCCAGGAGGGACACTACGT	ACGTTGGATGTGGCCAGCTTCTCCTCGATG
rs180287	ACGTTGGATGTTGTCTGCAGAATTACCTAT	ACGTTGGATGGAAAAAGAAAAAAAATCAG
rs338877	ACGTTGGATGCGTGGATGGAAATTTACATT	ACGTTGGATGTTCTTTGGATCAATGTTGCC
rs650665	ACGTTGGATGCCCATCTTACTCTATGATCTC	ACGTTGGATGAAAGTGCTGGGATTATAGGC
rs193419	ACGTTGGATGGCAAATCCAAAGACACAGGG	ACGTTGGATGATGTTTTTCATCACCCAGTG
rs180288	ACGTTGGATGTGTGACCTGGTAGCTTAGAG	ACGTTGGATGTTGTAGGAGGTCAGAAGAGG
rs186834	ACGTTGGATGTAAGCTACCAGGTCACACAC	ACGTTGGATGAGTTGATAGGAGAGTCAGGC
rs189266	ACGTTGGATGTAAGCTACCAGGTCACACAC	ACGTTGGATGAGTTGATAGGAGAGTCAGGC
rs189267	ACGTTGGATGCCTCATTGTGCCCTGTTGTG	ACGTTGGATGCTCTGCCTGACTCTCCTATC
rs170937	ACGTTGGATGCCTATCAACTGTTGATGGCG	ACGTTGGATGTTCCCTATTGTGCCCTGTTG
rs463263	ACGTTGGATGTACTGGACCCCTTTGCACAG	ACGTTGGATGTGCCCATGCTCATGTGTTGG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs463262	ACGTTGGATGTGCCCATGCTCATGTGTTGG	ACGTTGGATGACCCCTTTGCACAGATGCTG
rs460454	ACGTTGGATGAAGAAGGACCGTGTCAGAGA	ACGTTGGATGACATGAGCATGGGCAGGTAC
rs460455	ACGTTGGATGACATGAGCATGGGCAGGTAC	ACGTTGGATGAAGAAGGACCGTGTCAGAGA
rs460505	ACGTTGGATGACCGTGGACAGCGTCTCTGA	ACGTTGGATGTGCTCTGAGGGCAGAACAAAG
rs931316	ACGTTGGATGATGCACACACCCATGGTCAG	ACGTTGGATGCGGTTCACTCCAGCATTTCC
rs463431	ACGTTGGATGTCACCACAGCCCATGGGGA	ACGTTGGATGTTTGAAGCTCACAATGTGGG
rs461542	ACGTTGGATGTGATGAAGGCCAAGAATGCT	ACGTTGGATGTGTGTCCAGAACGTCAGGTG
rs463557	ACGTTGGATGTGATGAAGGCCAAGAATGCT	ACGTTGGATGTGTGTCCAGAACGTCAGGTG
rs191453	ACGTTGGATGCATCCAACAGCTCTGTCTGC	ACGTTGGATGACCCATCTGTAGCGCATCAG
rs2271212	ACGTTGGATGAGCTTCCCCGGAGGCAACGA	ACGTTGGATGTGCAGGTCTCGGCCAAAGAC
rs462009	ACGTTGGATGCAGGCTCCTCCTCGTTGCC	ACGTTGGATGTTGGTGTCCACGTGGTGT
rs2271211	ACGTTGGATGTCGTACCCCTGCTCTGGACG	ACGTTGGATGACTGACGCCCAGGGCCGCTT
rs396474	ACGTTGGATGTGGGAGTTGGAGATGATGAG	ACGTTGGATGTTCTCAGATCCCAGTCAAG
rs428901	ACGTTGGATGTCAGTGACAGAGCGAGACTC	ACGTTGGATGGGGCTCGATAATGTAGCCAT
rs452300	ACGTTGGATGAGCACAAGCTGAAGAGGTCT	ACGTTGGATGAGGAGAGAAGTGACAGATC
rs670256	ACGTTGGATGTAGCTCTATTCTTCCACCCC	ACGTTGGATGAGCGAGACTCCGTCTCAAAA

TABLE 34

dbSNP rs#	Extend Primer	Term Mix
rs2278221	CAAACGCTGAGGAGAAGCC	ACT
rs1650358	AAGAGACAAAAGGCCGGGC	ACT
rs1643818	TACAGGTGTGAACCACCGC	ACT
rs3733916	AGGCTGTAGTGTGACAGAC	ACG
rs1624933	GTCTCAAACCTCCTGACCTCA	ACT
rs1624857	AGACCAGCCTGGCCAACAT	ACT
rs1624832	GGCCAACATGGTGAAACCC	ACG
rs1624829	TGGCCAACATGGTGAAACCTT	ACT
rs2161171	TGGAATAAGAGCCCTGCAGTGG	ACT
rs1530499	CCCCTGCCCCAGCCACAGGAA	ACT
rs888764	ATGTTGTATTGGCTATATTTGTCA	ACG
rs873987	AAAACCTAAAAGAATCCACGGTA	ACG
rs4078699	GACACATGATTAACAGCAAACAAT	ACT
rs870311	AAGGGCGTGACGGCCCC	ACT
rs1643817	GAAAGGGGAGAAAAGATTATCCC	CGT
rs1643816	AGGACCAGGAGTTTCCCATTIT	ACT
rs1650355	GAATCAATGAAGAAGAGAGCTT	ACT
rs888763	GGTCAGGAGGCAGAGGGA	ACT
rs1862212	GGGGTGAAAGGGAGCAGGG	CGT
rs1110514	CAGGCCCCAGGTGAGGAA	CGT
rs3797600	CTTTGTTGGTTAACCAAACCC	ACG
rs3797602	GCTGACAGCTCCGGACATG	ACT
rs3797603	TGTCATTCTCCTTGTGAACCCTC	ACT
rs3776819	CCATTCCATTGCACCTGCATG	ACT
rs252076	CAAAGTGCTGGGATTGCAGG	ACG
rs252075	GAGCATTTGCAGGCATGCCCTCT	ACT
rs252074	CTGGGTGGCTGCTGGGC	ACG
rs252068	GGAAGGGTTTAAGCAAGGAG	ACT
rs252069	TGAGCACCTACTATGGGCTAG	ACT

dbSNP rs#	Extend Primer	Term Mix
rs194040	ATTCCATATCTTCAAAGTGATTCA	ACG
rs252070	CCTGGGCTTCCCCTCCC	ACG
rs3797606	AGCCCTTGGCCTCTCTCC	ACT
rs171667	CGCCTTTTGCTTATGCAAAGA	ACG
rs187539	AACCTTCAGGAAAGTTCCCAT	ACT
rs3836834	TCAAAATATCAAACCTACCATGAAA	ACG
rs252071	ACCCTGAGACACAGGGACT	ACT
rs252072	GCTGGGTCACACTCGCGGA	ACG
rs252073	GCCGAGAAAAGTCAGGGATTCT	ACT
rs379589	CGGGAGTACTGAGCACCCAGG	CGT
rs2052472	CCCCACTGTGACTATCTCCAC	ACT
rs2052471	GTCTCCTTTGGCTGCCAAG	ACT
rs2052470	TGCCAAGGCCCTGTCTC	ACT
rs2052469	CGCGGGGAAGTACTCGGC	ACT
rs3797608	GTCTCCTGTTCTGAGGCC	ACT
rs3797609	GGCAGAGCGGATGGCCTG	ACG
rs3822601	GTGAGGCCTGAGATGAGAACC	ACG
rs153131	TCCCATACTCCTGTGCTC	ACG
rs751546	CCGTTCTACAGCGTTAAGA	ACT
rs2279979	GGCCACCAGACAGATGTAAG	ACT
rs252060	CGTGTTTCGGCAGAGGTGA	ACT
rs3797610	CTTCTCCCTTGGGTGATGTGTT	ACT
rs194039	CCACCGTGCCGGGACATTTTTTTT	ACT
rs168773	ACTGGAGATATCACGGGAGC	CGT
rs252061	CCAGCTGGTCACAGGGCTCCC	ACG
rs187537	TCATGCTAAGTGAAATAAGCCA	ACT
rs252062	GCCACCACCGTCCACAGA	CGT
rs2431255	CTGTATATTTACCGCAATTAAAA	ACT
rs3797612	GGCATTATCGTCAGGGCAA	ACG
rs3797613	CCGCCGCCGGTCTCCCA	ACG
rs614114	GAACGTTCTCTCACTTTTGCC	ACT
rs252063	CTCCCGTCCTCTGAGCCTT	ACT
rs252064	GAAACTAAGGCTCAGAGGAC	ACT
rs252065	TGGAAAAGGCGAGGCCTGGAGT	ACG
rs450502	GGAAAAGGCGAGGCCTGGAGTT	ACT
rs439252	GCCTCCCAAAGTGCTGGGATTA	ACG
rs252066	TAGCCCTCTGGAGCCCAG	ACG
rs457957	GGGCCCTCCTTAAAGCTC	ACT
rs3797614	TGGCCCTCGCTCTAATGCA	ACG
rs423552	CTCGATGTTGTAGTCATCGTC	ACG
rs398829	TGGCGTGCTCCTCTAGGA	ACG
rs416646	CTCAGCAGGTCTGATCCATC	ACT
rs187450	GGGCAGACTCCCCAGGAT	ACT
rs337807	GCAGGCCACTCGGTGGAC	ACT
rs337806	CCACCCAGGGGTAGCCC	ACT
rs1396438	GGCAGGCAGGTGGCCTG	ACT
rs1396437	CGGCAGAAGCAGCCTCAAGA	ACG
rs2411811	ACATAATTTCCAAATTTACCCC	CGT
rs2898813	GGTCCTGGGTGGAGGGAT	ACT

dbSNP rs#	Extend Primer	Term Mix
rs189256	AGCAAGGCTCTATTTGGGGA	ACT
rs173072	CTTTGCTCACATCGTGGCCAAA	ACT
rs337805	GGAGCAGGAAAATTACATGACT	ACG
rs191415	GAGTCCAACGTTGTCCACAT	ACT
rs180045	ACTTGTTTCTACAATTCTCATT	ACG
rs189255	GACTCAGTCCCAGGTTTTCT	ACT
rs652766	AGAAAACCTGGGACTGAGTCT	ACT
rs466750	TCCTTAAATGCCTTGGTTGGCAAT	ACT
rs442406	TTCTGGCTGTTGGGTTTGAAC	ACT
rs662407	AAACATCTGAAATTAAGCACC	ACT
rs592971	AGCATTTCTTTGACTGCTCTTTCA	ACT
rs457187	GGAGTATCTGTTCTTGTGG	ACT
rs459490	TTGAACATAGGAATAACCCGC	ACT
rs459668	GTCTTCTTTTGTGTTTTTGGAGA	ACG
rs462646	ATTATTCGACGGAGATTATTTGAC	ACT
rs458272	ATTATTTTTCTGTCTGGTGTGG	ACT
rs463455	CCTCCTCATTGTCATTCTTTTC	ACT
rs675880	CTTTCATGACATTGACACAACACTAC	ACT
rs810617	CCACAGCCTCCGCCTCCC	ACT
rs464156	GGGTTTCCAGGTTAAATGGC	ACT
rs458083	CTCCTGCTCTGCCTATCCTT	ACT
rs467333	ATTCTTCCCCTCCTGCTCT	ACT
rs465381	GCCTCCCACAGTTCCCTTGTT	ACT
rs466363	GTGATGGCTCTGCACCAGA	ACG
rs2457099	AGCGTGTGCCAGCTCTCC	ACT
rs463901	GACACAATTCAGAGCGACTTAC	ACT
rs465621	AAGTGCTAGAAGAAAATGTAGC	ACT
rs463724	CCTTGCGCCATCCCCTAG	CGT
rs465242	TGTGCCCATCCCCCCTT	ACT
rs467419	AACGTAAGTCCTAATGACCGCCC	ACG
rs456135	CCCTCTCCTCTTCTGGGCA	ACT
rs464536	GCTTTGGTCTCCTGAGCC	ACG
rs461898	CACAGAGCGACTCTCTTTGGTT	ACT
rs389558	CTGACAGTTCTCTAAACTCCCA	ACG
rs466752	TTCTTTTTCTCCCTGAAGCA	ACG
rs455655	CACCCCATATGGCTCATGGG	ACT
rs463435	GGGAAGGAGGTACTTAGCAG	ACG
rs2174971	GTGCCACTCTCCAGCGGCC	ACG
rs1979979	TTGCCGGCCCCACCTC	ACG
rs411804	GAAAATCCCTGTCACCAGTC	ACG
rs1623885	CTTGGCTGCAGCACCCCA	ACT
rs1643811	GCCCTGGTACTTTCAGCTCCCT	ACG
rs434430	GTGTGCATGTGTGTGCCTG	CGT
rs187538	TAAACGGGCCAAAAACGCCTAT	ACT
rs252067	GCGCCTACGGATGTCAGG	ACT
rs459319	CATGTTGAACAGAGAGAAACGGTC	ACG
rs467289	TCACTGAGAAATATTTTGCTCCC	ACT
rs462644	GGTGAGCCCTTGGCTGTG	ACG
rs458752	TAAAGCGCTCTTACAAATCAACA	ACT

dbSNP rs#	Extend Primer	Term Mix
rs708320	TGGTGAATCCTGTCTCTACTAAA	CGT
rs457954	CACCGTTTCTTATAATGCAGCC	ACT
rs2411810	GGGGACGTTACTTCTTTTCAC	ACG
rs3084687	ATTTATATATGTGTGTGTACACAT	ACT
rs69638	CCCATTGGCTGTCCTGGAA	ACT
rs455452	CCTCAACCCCAGATGCCCTC	ACG
rs464850	ACTCCTGCCTGAGTGTCTC	ACT
rs431472	GTGAAGCGGAAGGAGACTC	ACG
rs2411809	CTGCACACCCTCTGCACAG	ACG
rs2457094	TGGCTGGCACCCTGCACTGC	ACT
rs2457095	TGGCTCATGCTTCTAATCCCA	ACT
rs2261740	CTGCACTCCAGCCTGGGC	ACT
rs1109180	ACATCAGTGACAGTGTAAATGGTA	ACG
rs1109179	TATGCAGACCCCCTCCCC	ACT
rs1109178	AACAACAGCAACAGAAATGAAG	ACT
rs456909	CGATTCCCACGCGTGTCTG	ACG
rs469124	CCTGGCTCCATTGGTGTGAA	ACT
rs468039	CCTTCACACCAATGGAGCCAG	ACT
rs467017	CTGCCACTAAACAGATGAGAA	ACT
rs469290	ATTTCTGGGCCCAAAGTCCA	ACT
rs469090	CCAATTGTTCCAGCCACTCCC	ACT
rs469568	TGATATTGCTTGCTTGGGTCTTAG	ACT
rs468386	GGTCAAGAATTCAAGAGCAGC	ACT
rs469349	GTGCAGTGGCAGATCCTA	ACT
rs469099	GCAGGTGGAACCGCAGAC	ACT
rs456868	GGAGCTGCGGTGACTCCC	ACT
rs465389	CCCTGGCACTCGCAGACC	ACT
rs463892	AGCTCCCCCGCACCAC	ACT
rs468548	AAGGGAACATGCAAGCAAAGACTC	ACT
rs654612	TGCAAGCAAAGACTCGAATGA	ACT
rs468542	TCACTCACTTGATTCTGCCATC	ACT
rs469262	CACTGTGGGATTTCCAGCAGA	ACT
rs708323	TATACAGGTCACCCATTTAAAGT	ACT
rs469089	CCTCGGCCTTCCCCAGCT	ACT
rs469396	AATGAGGGAACCTGCAGTTTAAGA	ACT
rs468723	CAGACCCCATGCCTTGCC	ACT
rs467604	GAGTTTCCTCCTCTTTCACAA	ACT
rs338874	CACAGCCACTGGGGAGTAG	ACT
rs338875	TTGCTCGCGTGTGCCAGCAAAT	ACG
rs1385803	AAGTGGAATTCTCATGGCAGAT	ACT
rs1385804	CATTCCAGAAGTGGAATTCTCATG	ACT
rs338876	AGGAAGGTGCTCCGGCCT	ACG
rs189803	TGCTTCCCCCTTCCCCCT	CGT
rs452215	TCTATTCTTCCACCCCCATCTT	ACT
rs641170	CTATTCTTCCACCCCCATCT	ACT
rs584398	CTCTTATATAGCTCTATTCTTCC	CGT
rs385330	AGGTGTCTGCAGATAATACATT	ACG
rs429538	CCTGGGGCACAGGACAATA	ACT
rs371229	GACAATAGTTGGGGCAAGAC	ACT

dbSNP rs#	Extend Primer	Term Mix
rs460874	ACAAAACATATCCTTCAAAAATACA	CGT
rs646121	GTTTTTGTTTCTCTGAAAGTGTCT	CGT
rs468262	CACCCAACACTTGCTCCC	ACG
rs467863	GCTGATGGGAGGCCAATGT	ACT
rs191434	GTCCAGAGATCCTGCTCACT	CGT
rs2054782	CCCCCTCCATCACCTCCC	ACG
rs468499	GTGAGCCAGCAATTCTCCTA	ACT
rs180287	CAATGATCAGAACTCAGAGGTTTT	ACT
rs338877	AGAGATAAATTTCCAGTGTGAG	CGT
rs650665	AGACATCCCGGCCGGGC	ACT
rs193419	CCAAAGACACAGGGAGTAGATTA	ACT
rs180288	GAGAATATTCTTGTGGGCTTAAT	ACT
rs186834	CCAGGTCACACACACTC	ACG
rs189266	CACACACTCCCTCTCACTGT	ACT
rs189267	TTCTGTGCATCTTTGACGCCATC	CGT
rs170937	GATGGCGTCAAAGATGCACA	ACT
rs463263	CCCCTTTGCACAGATGCTG	ACT
rs463262	GGGGAGCAGCCAGTTCCTA	ACT
rs460454	AGAGGCTGGGGACAGAGAA	ACT
rs460455	GGTACCCACCAGTCTCCTTCT	ACT
rs460505	CAGCGTCTCTGACACGGTC	ACG
rs931316	GGTCAGAGCAGACACATCCACAT	ACG
rs463431	CCCATGGGGAGCACCAAG	ACT
rs461542	TGGGAGCTCCCGGGATATTGCC	ACG
rs463557	GCTCCCGGGATATTGCCCA	ACT
rs191453	CTGGGCTGGGGCCCTGC	ACT
rs2271212	CGAGGAGGAGCCTGGCAG	ACG
rs462009	CTCCTCGTTGCCTCCGGG	ACT
rs2271211	GACGTAGCTGCCGACACCA	ACG
rs396474	CTGGTGGCCCATCTATCCTGG	ACT
rs428901	GAGCGAGACTCCGTCTCAA	CGT
rs452300	CTGAAGAGGTCTTTCTCCTTCC	CGT
rs670256	TTCTTCCACCCCCATCTTTG	ACT

Genetic Analysis

[0284] Allelotyping results from the discovery cohort are shown for cases and controls in Table 35. The allele frequency for the A2 allele is noted in the fifth and sixth columns for osteoarthritis case pools and control pools, respectively, where “AF” is allele frequency. The allele frequency for the A1 allele can be easily calculated by subtracting the A2 allele frequency from 1 ($A1\ AF = 1 - A2\ AF$). For example, the SNP rs2278221 has the following case and control allele frequencies: case A1 (C) = 0.36; case A2 (T) = 0.64; control A1 (C) = 0.37; and control A2 (T) = 0.63, where the nucleotide is provided in paranthesis. Some SNPs are labeled “untyped” because of failed assays.

TABLE 35

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs2278221	210	178695460	C/T	0.64	0.63	0.770
rs1650358	3608	178698858	C/G			
rs1643818	3609	178698859	C/G			
rs3733916	4318	178699568	C/T			
rs1624933	5593	178700843	A/G	0.69	0.71	0.255
rs1624857	5629	178700879	C/T	0.79	0.81	0.574
rs1624832	5639	178700889	A/G	0.41	0.44	0.203
rs1624829	5640	178700890	C/T	0.89	0.93	0.044
rs2161171	8943	178704193	A/C			
rs1530499	17968	178713218	A/G	0.39	0.39	0.861
rs888764	19887	178715137	A/G			
rs873987	21034	178716284	A/G			
rs4078699	21085	178716335	C/T	0.56	0.54	0.374
rs870311	21596	178716846	A/G	0.51	0.50	0.590
rs1643817	23379	178718629	A/C	0.27	NA	NA
rs1643816	23432	178718682	A/C			
rs1650355	24007	178719257	A/C			
rs888763	26121	178721371	A/G	0.40	0.42	0.390
rs1862212	26273	178721523	A/T	0.55	0.54	0.753
rs1110514	26755	178722005	A/T	0.29	0.28	0.572
rs3797600	27411	178722661	C/T	0.56	0.57	0.738
rs3797602	27710	178722960	G/T	0.65	0.64	0.564
rs3797603	27842	178723092	C/T			
rs3776819	28379	178723629	C/T	0.46	0.46	0.850
rs252076	29603	178724853	C/T	0.46	0.48	0.519
rs252075	31232	178726482	C/G	0.35	0.36	0.859
rs252074	31504	178726754	A/G	0.35	0.34	0.816
rs252068	32583	178727833	C/G	0.47	0.48	0.656
rs252069	32794	178728044	A/G	0.28	0.27	0.626
rs194040	32840	178728090	C/T	0.31	0.32	0.665
rs252070	33044	178728294	C/T	0.58	0.57	0.573
rs3797606	33150	178728400	A/C	0.88	0.88	0.684
rs171667	33218	178728468	A/G	0.48	0.51	0.166
rs187539	33513	178728763	C/T	0.33	0.34	0.652
rs3836834	33959	178729209	- TATCA AACTAC CATGAA A			
rs252071	34486	178729736	A/G	0.30	0.31	0.666
rs252072	36289	178731539	C/T	0.49	0.50	0.677
rs252073	36570	178731820	C/T			
rs379589	38247	178733497	A/T	0.59	0.63	0.096
rs2052472	38477	178733727	A/C	0.05	0.06	0.508
rs2052471	38518	178733768	C/T	0.89	0.88	0.459
rs2052470	38529	178733779	C/T	0.83	0.80	0.125
rs2052469	38667	178733917	A/G	0.83	0.80	0.172
rs3797608	39781	178735031	C/T	0.06	0.07	0.578
rs3797609	39856	178735106	C/T	0.05	0.05	0.812
rs3822601	39927	178735177	C/T	0.08	0.08	0.802
rs153131	40506	178735756	A/G	0.76	0.77	0.944
rs751546	41869	178737119	C/G	0.93	0.92	0.585
rs2279979	42452	178737702	C/T	0.93	0.92	0.436
rs252060	44788	178740038	C/T	0.81	0.82	0.760
rs3797610	46059	178741309	A/C	0.17	0.17	0.858
rs194039	46846	178742096	A/G	0.41	0.47	0.035
rs168773	47712	178742962	A/T	0.35	0.38	0.266
rs252061	48796	178744046	C/T	0.21	0.19	0.508
rs187537	49441	178744691	C/G			
rs252062	49602	178744852	A/T	0.95	0.95	0.960
rs2431255	49723	178744973	A/C	0.24	0.19	0.034
rs3797612	50050	178745300	C/T	0.38	0.43	0.036

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3797613	50171	178745421	C/T	0.21	0.21	0.941
rs614114	50477	178745727	C/T	0.50	0.53	0.387
rs252063	50818	178746068	C/T	0.57	0.55	0.313
rs252064	50833	178746083	C/T	0.52	0.52	0.806
rs252065	50881	178746131	A/G	0.22	0.22	0.857
rs450502	50882	178746132	A/G			
rs439252	51386	178746636	C/T			
rs252066	51534	178746784	C/T	0.19	0.18	0.618
rs457957	52317	178747567	A/G	0.67	0.70	0.172
rs3797614	52368	178747618	C/T			
rs423552	52970	178748220	A/G	0.90	0.92	0.215
rs398829	53023	178748273	A/G			
rs416646	53356	178748606	A/G	0.56	0.57	0.650
rs187450	53882	178749132	G/T			
rs337807	54553	178749803	C/T	0.55	0.59	0.208
rs337806	55475	178750725	A/C	0.11	0.10	0.925
rs1396438	55530	178750780	A/G	0.56	0.54	0.494
rs1396437	55691	178750941	C/T			
rs2411811	55848	178751098	A/C			
rs2898813	55879	178751129	C/G			
rs189256	56316	178751566	A/G	0.19	0.19	0.988
rs173072	56911	178752161	A/C			
rs337805	57320	178752570	A/G	0.25	0.24	0.657
rs191415	57391	178752641	C/T			
rs180045	57437	178752687	C/T	0.51	0.47	0.211
rs189255	57478	178752728	C/G	0.15	0.12	0.273
rs652766	57500	178752750	C/T	0.57	0.61	0.213
rs466750	59111	178754361	G/T	0.35	0.33	0.493
rs442406	59333	178754583	A/G	0.57	0.59	0.420
rs662407	59715	178754965	A/G	0.31	0.27	0.102
rs592971	59804	178755054	A/G			
rs457187	59851	178755101	A/G	0.23	0.24	0.842
rs459490	59929	178755179	C/T	0.21	0.20	0.604
rs459668	60052	178755302	C/T	0.20	0.19	0.648
rs462646	60240	178755490	C/T	0.43	0.43	0.905
rs458272	60359	178755609	G/T	0.22	0.20	0.523
rs463455	60381	178755631	A/G	0.25	0.24	0.644
rs675880	60456	178755706	C/T	0.63	0.65	0.591
rs810617	60724	178755974	C/G			
rs464156	60875	178756125	C/T	0.34	0.34	0.892
rs458083	60968	178756218	A/G	0.80	0.82	0.499
rs467333	60978	178756228	C/G	0.11	0.12	0.369
rs465381	60998	178756248	C/T			
rs466363	61557	178756807	C/T	0.31	0.34	0.358
rs2457099	62091	178757341	C/T	0.44	0.44	0.956
rs463901	62645	178757895	C/T	0.43	0.45	0.395
rs465621	62943	178758193	A/C	0.62	0.63	0.534
rs463724	63131	178758381	A/T	0.09	0.08	0.523
rs465242	63145	178758395	G/T			
rs467419	63406	178758656	A/G	0.65	0.66	0.647
rs456135	63427	178758677	C/G	0.79	0.80	0.686
rs464536	63554	178758804	C/T	0.36	0.34	0.296
rs461898	63661	178758911	A/G	0.30	0.32	0.411
rs389558	64093	178759343	A/G	0.24	0.26	0.325
rs466752	64153	178759403	C/T	0.35	0.37	0.446
rs455655	64409	178759659	C/G	0.87	0.89	0.536
rs463435	64544	178759794	C/T	0.68	0.66	0.428
rs2174971	65257	178760507	C/T	0.52	0.51	0.695
rs1979979	65626	178760876	A/G	0.07	0.06	0.692
rs411804	65739	178760989	A/G	0.78	0.78	0.976
rs1623885	66392	178761642	C/T	0.82	0.80	0.492
rs1643811	66720	178761970	C/T	0.24	0.24	0.924
rs434430	69177	178764427	A/T			
rs187538	69336	178764586	G/T			

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs252067	69636	178764886	A/G	0.21	0.23	0.606
rs459319	69823	178765073	A/G	0.19	0.20	0.640
rs467289	69928	178765178	C/T	0.26	0.26	0.988
rs462644	70547	178765797	C/T	0.59	0.58	0.914
rs458752	70633	178765883	C/T	0.18	0.20	0.513
rs708320	71805	178767055	A/C			
rs457954	72181	178767431	C/G	0.71	0.73	0.327
rs2411810	72200	178767450	C/T	0.28	0.26	0.252
rs3084687	72474	178767724	-IAT	0.13	0.12	0.884
rs69638	72567	178767817	C/G	0.54	0.52	0.449
rs455452	72973	178768223	A/G	0.59	0.60	0.733
rs464850	73468	178768718	A/G	0.11	0.09	0.249
rs431472	73889	178769139	A/G	0.33	0.34	0.713
rs2411809	75730	178770980	C/T			
rs2457094	75970	178771220	A/G	0.71	0.73	0.383
rs2457095	76114	178771364	A/G	0.74	0.76	0.551
rs2261740	76342	178771592	C/T	0.35	0.36	0.702
rs1109180	76449	178771699	A/G			
rs1109179	76465	178771715	C/T			
rs1109178	76791	178772041	A/C	0.46	0.45	0.820
rs456909	78042	178773292	A/G	0.55	0.53	0.444
rs469124	80758	178776008	A/G			
rs468039	80778	178776028	C/T			
rs467017	81356	178776606	A/C	0.33	0.32	0.665
rs469290	81576	178776826	A/G	0.57	0.57	0.871
rs469090	81689	178776939	C/T	0.82	0.83	0.387
rs469568	81759	178777009	G/T	0.38	0.38	0.888
rs468386	81950	178777200	C/G			
rs469349	82562	178777812	A/C			
rs469099	83591	178778841	C/T	0.66	0.63	0.264
rs456868	83700	178778950	A/G			
rs465389	83821	178779071	C/G			
rs463892	83842	178779092	C/G			
rs468548	83923	178779173	G/T			
rs654612	83929	178779179	A/C			
rs468542	84021	178779271	C/G			
rs469262	84175	178779425	C/T	0.45	0.47	0.405
rs708323	84417	178779667	A/G	0.73	0.69	0.138
rs469089	84747	178779997	C/G			
rs469396	85746	178780996	C/G	0.38	0.37	0.817
rs468723	86129	178781379	C/T	0.37	0.38	0.754
rs467604	86335	178781585	A/G	0.34	0.32	0.504
rs338874	87315	178782565	C/G	0.43	0.44	0.879
rs338875	87648	178782898	A/G	0.48	0.50	0.289
rs1385803	87764	178783014	A/C			
rs1385804	87770	178783020	C/G			
rs338876	88221	178783471	C/T	0.39	0.39	0.889
rs189803	90474	178785724	A/C			
rs452215	91148	178786398	G/T			
rs641170	91150	178786400	G/T			
rs584398	91160	178786410	G/T			
rs385330	91733	178786983	C/T			
rs429538	91772	178787022	A/C			
rs371229	91785	178787035	C/T			
rs460874	93140	178788390	A/T	0.74	0.71	0.351
rs646121	93148	178788398	A/T	0.93	0.94	0.687
rs468262	96080	178791330	A/G			
rs467863	96157	178791407	C/G			
rs191434	96313	178791563	A/C			
rs2054782	96759	178792009	C/T	0.44	0.42	0.353
rs468499	97026	178792276	A/C			
rs180287	97320	178792570	C/G			
rs338877	97732	178792982	A/T	0.04	0.04	0.863
rs650665	98713	178793963	C/G			

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs193419	99707	178794957	A/C			
rs180288	99959	178795209	C/G			
rs186834	100009	178795259	A/G			
rs189266	100020	178795270	C/G			
rs189267	100065	178795315	A/C			
rs170937	100086	178795336	C/G			
rs463263	101270	178796520	C/G			
rs463262	101276	178796526	G/T			
rs460454	101371	178796621	C/T			
rs460455	101376	178796626	C/G			
rs460505	101439	178796689	C/T			
rs931316	101820	178797070	C/T			
rs463431	102392	178797642	C/G			
rs461542	102602	178797852	A/G			
rs463557	102604	178797854	A/C			
rs191453	102896	178798146	C/T	0.11	0.14	0.123
rs2271212	189104	178884354	C/T	0.65	0.57	0.003
rs462009	189134	178884384	C/T			
rs2271211	189205	178884455	A/G			
rs396474	Not mapped	Not mapped	A/C			
rs428901	Not mapped	Not mapped	A/T	0.64	0.72	0.015
rs452300	Not mapped	Not mapped	G/T			
rs670256	Not mapped	Not mapped	G/T			

[0285] The *ADAMTS2* proximal SNPs were also allelotyped in the replication cohorts using the methods described herein and the primers provided in Tables 33 and 34. The replication allelotyping results for replication cohort #1 and replication cohort #2 are provided in Tables 36 and 37, respectively.

TABLE 36

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs2278221	210	178695460	C/T	0.64	0.62	0.624
rs1650358	3608	178698858	C/G			
rs1643818	3609	178698859	C/G			
rs3733916	4318	178699568	C/T			
rs1624933	5593	178700843	A/G	0.65	0.69	0.322
rs1624857	5629	178700879	C/T	0.81	untyped	NA
rs1624832	5639	178700889	A/G	0.38	0.42	0.265
rs1624829	5640	178700890	C/T	0.87	untyped	NA
rs2161171	8943	178704193	A/C			
rs1530499	17968	178713218	A/G	0.39	0.40	0.765
rs888764	19887	178715137	A/G			
rs873987	21034	178716284	A/G			
rs4078699	21085	178716335	C/T	0.55	0.54	0.733
rs870311	21596	178716846	A/G	0.50	0.50	0.828
rs1643817	23379	178718629	A/C	0.27	untyped	
rs1643816	23432	178718682	A/C			
rs1650355	24007	178719257	A/C			
rs888763	26121	178721371	A/G	0.40	0.40	0.816
rs1862212	26273	178721523	A/T	0.55	0.55	0.936
rs1110514	26755	178722005	A/T	0.29	0.29	0.997
rs3797600	27411	178722661	C/T	0.57	0.58	0.604
rs3797602	27710	178722960	G/T	0.64	0.63	0.879
rs3797603	27842	178723092	C/T			
rs3776819	28379	178723629	C/T	0.47	0.46	0.889
rs252076	29603	178724853	C/T	0.46	0.49	0.410
rs252075	31232	178726482	C/G	0.35	0.37	0.572

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs252074	31504	178726754	A/G	0.35	0.35	0.914
rs252068	32583	178727833	C/G	0.48	0.48	0.853
rs252069	32794	178728044	A/G	0.29	0.28	0.765
rs194040	32840	178728090	C/T	0.31	0.33	0.450
rs252070	33044	178728294	C/T	0.57	0.58	0.609
rs3797606	33150	178728400	A/C	0.87	0.91	0.119
rs171667	33218	178728468	A/G	0.45	0.50	0.125
rs187539	33513	178728763	C/T	0.33	0.34	0.709
rs3836834	33959	178729209	- /TATCA AACTAC CATGAA A			
rs252071	34486	178729736	A/G	0.30	0.32	0.566
rs252072	36289	178731539	C/T	0.48	0.51	0.400
rs252073	36570	178731820	C/T			
rs379589	38247	178733497	A/T	0.59	0.65	0.035
rs2052472	38477	178733727	A/C	0.04	0.06	0.493
rs2052471	38518	178733768	C/T	0.87	0.88	0.697
rs2052470	38529	178733779	C/T	0.84	0.78	0.036
rs2052469	38667	178733917	A/G	0.84	0.79	0.086
rs3797608	39781	178735031	C/T	0.06	0.07	0.530
rs3797609	39856	178735106	C/T	0.04	0.05	0.841
rs3822601	39927	178735177	C/T	0.08	0.08	0.904
rs153131	40506	178735756	A/G	0.77	0.77	0.964
rs751546	41869	178737119	C/G	0.94	0.92	0.265
rs2279979	42452	178737702	C/T	0.94	0.92	0.238
rs252060	44788	178740038	C/T	0.82	0.80	0.553
rs3797610	46059	178741309	A/C	0.16	0.18	0.459
rs194039	46846	178742096	A/G	0.43	0.45	0.589
rs168773	47712	178742962	A/T	0.34	0.35	0.845
rs252061	48796	178744046	C/T	0.23	0.22	0.884
rs187537	49441	178744691	C/G			
rs252062	49602	178744852	A/T	0.98	0.96	0.310
rs2431255	49723	178744973	A/C	0.24	0.19	0.108
rs3797612	50050	178745300	C/T	0.42	0.46	0.254
rs3797613	50171	178745421	C/T	0.19	0.21	0.576
rs614114	50477	178745727	C/T	0.52	0.54	0.717
rs252063	50818	178746068	C/T	0.55	0.57	0.537
rs252064	50833	178746083	C/T	0.52	0.50	0.609
rs252065	50881	178746131	A/G	0.21	0.25	0.234
rs450502	50882	178746132	A/G			
rs439252	51386	178746636	C/T			
rs252066	51534	178746784	C/T	0.20	0.20	0.883
rs457957	52317	178747567	A/G	0.66	0.71	0.162
rs3797614	52368	178747618	C/T			
rs423552	52970	178748220	A/G	0.90	0.92	0.380
rs398829	53023	178748273	A/G			
rs416646	53356	178748606	A/G	0.58	0.59	0.915
rs187450	53882	178749132	G/T			
rs337807	54553	178749803	C/T	0.60	NA	NA
rs337806	55475	178750725	A/C	0.10	0.10	0.997
rs1396438	55530	178750780	A/G	0.52	0.57	0.188
rs1396437	55691	178750941	C/T			
rs2411811	55848	178751098	A/C			
rs2898813	55879	178751129	C/G			
rs189256	56316	178751566	A/G	0.21	0.20	0.852
rs173072	56911	178752161	A/C			
rs337805	57320	178752570	A/G	0.24	0.24	0.950
rs191415	57391	178752641	C/T			
rs180045	57437	178752687	C/T	0.47	0.46	0.918
rs189255	57478	178752728	C/G	0.14	0.13	0.764
rs652766	57500	178752750	C/T	0.59	0.61	0.570
rs466750	59111	178754361	G/T	0.38	0.37	0.606

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs442406	59333	178754583	A/G	0.56	0.57	0.882
rs662407	59715	178754965	A/G	0.32	0.27	0.134
rs592971	59804	178755054	A/G			
rs457187	59851	178755101	A/G	0.23	0.25	0.451
rs459490	59929	178755179	C/T	0.22	0.21	0.671
rs459668	60052	178755302	C/T	0.20	0.19	0.712
rs462646	60240	178755490	C/T	0.42	0.44	0.439
rs458272	60359	178755609	G/T	0.21	0.21	0.755
rs463455	60381	178755631	A/G	0.25	0.25	0.783
rs675880	60456	178755706	C/T	0.62	0.63	0.741
rs810617	60724	178755974	C/G			
rs464156	60875	178756125	C/T	0.32	0.34	0.541
rs458083	60968	178756218	A/G	0.80	0.82	0.499
rs467333	60978	178756228	C/G	0.10	0.13	0.243
rs465381	60998	178756248	C/T			
rs466363	61557	178756807	C/T	0.31	0.34	0.494
rs2457099	62091	178757341	C/T	0.45	0.45	0.997
rs463901	62645	178757895	C/T	0.46	0.46	0.852
rs465621	62943	178758193	A/C	0.64	0.63	0.853
rs463724	63131	178758381	A/T	0.09	0.08	0.737
rs465242	63145	178758395	G/T			
rs467419	63406	178758656	A/G	0.64	0.65	0.694
rs456135	63427	178758677	C/G	0.79	0.76	0.339
rs464536	63554	178758804	C/T	0.36	0.34	0.553
rs461898	63661	178758911	A/G	0.31	0.33	0.727
rs389558	64093	178759343	A/G	0.27	0.28	0.762
rs466752	64153	178759403	C/T	0.34	0.38	0.223
rs455655	64409	178759659	C/G	0.87	untyped	NA
rs463435	64544	178759794	C/T	0.65	0.65	0.973
rs2174971	65257	178760507	C/T	0.49	0.51	0.476
rs1979979	65626	178760876	A/G	0.08	0.07	0.579
rs411804	65739	178760989	A/G	0.77	0.79	0.420
rs1623885	66392	178761642	C/T	0.81	0.78	0.451
rs1643811	66720	178761970	C/T	0.26	0.25	0.715
rs434430	69177	178764427	A/T			
rs187538	69336	178764586	G/T			
rs252067	69636	178764886	A/G	0.22	0.22	0.978
rs459319	69823	178765073	A/G	0.19	0.22	0.245
rs467289	69928	178765178	C/T	0.26	0.29	0.377
rs462644	70547	178765797	C/T	0.58	0.56	0.637
rs458752	70633	178765883	C/T	0.18	0.23	0.129
rs708320	71805	178767055	A/C			
rs457954	72181	178767431	C/G	0.69	0.73	0.143
rs2411810	72200	178767450	C/T	0.28	0.23	0.083
rs3084687	72474	178767724	-A/T	0.12	0.13	0.767
rs69638	72567	178767817	C/G	0.53	0.49	0.157
rs455452	72973	178768223	A/G	0.58	0.61	0.313
rs464850	73468	178768718	A/G	0.13	0.10	0.171
rs431472	73889	178769139	A/G	0.32	0.39	0.048
rs2411809	75730	178770980	C/T			
rs2457094	75970	178771220	A/G	0.70	0.75	0.157
rs2457095	76114	178771364	A/G	0.74	0.75	0.707
rs2261740	76342	178771592	C/T	0.34	untyped	NA
rs1109180	76449	178771699	A/G			
rs1109179	76465	178771715	C/T			
rs1109178	76791	178772041	A/C	0.47	0.48	0.715
rs456909	78042	178773292	A/G	0.56	0.54	0.537
rs469124	80758	178776008	A/G			
rs468039	80778	178776028	C/T			
rs467017	81356	178776606	A/C	0.33	0.31	0.480
rs469290	81576	178776826	A/G	0.63	0.66	0.427
rs469090	81689	178776939	C/T	0.80	0.83	0.300
rs469568	81759	178777009	G/T	0.39	0.43	0.234
rs468386	81950	178777200	C/G			

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs469349	82562	178777812	A/C			
rs469099	83591	178778841	C/T	0.66	0.60	0.066
rs456868	83700	178778950	A/G			
rs465389	83821	178779071	C/G			
rs463892	83842	178779092	C/G			
rs468548	83923	178779173	G/T			
rs654612	83929	178779179	A/C			
rs468542	84021	178779271	C/G			
rs469262	84175	178779425	C/T	0.46	0.50	0.232
rs708323	84417	178779667	A/G	0.72	0.66	0.071
rs469089	84747	178779997	C/G			
rs469396	85746	178780996	C/G	0.37	0.35	0.522
rs468723	86129	178781379	C/T	0.39	0.41	0.495
rs467604	86335	178781585	A/G	0.33	0.30	0.303
rs338874	87315	178782565	C/G	0.44	0.46	0.628
rs338875	87648	178782898	A/G	0.49	0.54	0.106
rs1385803	87764	178783014	A/C			
rs1385804	87770	178783020	C/G			
rs338876	88221	178783471	C/T	0.38	0.36	0.609
rs189803	90474	178785724	A/C			
rs452215	91148	178786398	G/T			
rs641170	91150	178786400	G/T			
rs584398	91160	178786410	G/T			
rs385330	91733	178786983	C/T			
rs429538	91772	178787022	A/C			
rs371229	91785	178787035	C/T			
rs460874	93140	178788390	A/T	0.74	0.69	0.118
rs646121	93148	178788398	A/T	0.93	0.95	0.477
rs468262	96080	178791330	A/G			
rs467863	96157	178791407	C/G			
rs191434	96313	178791563	A/C			
rs2054782	96759	178792009	C/T	0.45	0.42	0.514
rs468499	97026	178792276	A/C			
rs180287	97320	178792570	C/G			
rs338877	97732	178792982	A/T	0.04	0.04	0.781
rs650665	98713	178793963	C/G			
rs193419	99707	178794957	A/C			
rs180288	99959	178795209	C/G			
rs186834	100009	178795259	A/G			
rs189266	100020	178795270	C/G			
rs189267	100065	178795315	A/C			
rs170937	100086	178795336	C/G			
rs463263	101270	178796520	C/G			
rs463262	101276	178796526	G/T			
rs460454	101371	178796621	C/T			
rs460455	101376	178796626	C/G			
rs460505	101439	178796689	C/T			
rs931316	101820	178797070	C/T			
rs463431	102392	178797642	C/G			
rs461542	102602	178797852	A/G			
rs463557	102604	178797854	A/C			
rs191453	102896	178798146	C/T	0.15	0.19	0.139
rs2271212	189104	178884354	C/T	0.64	0.58	0.072
rs462009	189134	178884384	C/T			
rs2271211	189205	178884455	A/G			
rs396474	Not mapped	Not mapped	A/C			
rs428901	Not mapped	Not mapped	A/T	0.66	untyped	NA
rs452300	Not mapped	Not mapped	G/T			
rs670256	Not mapped	Not mapped	G/T			

TABLE 37

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs2278221	210	178695460	C/T	0.64	0.64	0.837
rs1650358	3608	178698858	C/G			
rs1643818	3609	178698859	C/G			
rs3733916	4318	178699568	C/T			
rs1624933	5593	178700843	A/G	0.73	0.75	0.447
rs1624857	5629	178700879	C/T	0.78	0.81	0.289
rs1624832	5639	178700889	A/G	0.44	0.47	0.423
rs1624829	5640	178700890	C/T	0.90	0.93	0.294
rs2161171	8943	178704193	A/C			
rs1530499	17968	178713218	A/G	0.39	0.36	0.499
rs888764	19887	178715137	A/G			
rs873987	21034	178716284	A/G			
rs4078699	21085	178716335	C/T	0.57	0.54	0.316
rs870311	21596	178716846	A/G	0.52	0.50	0.579
rs1643817	23379	178718629	A/C			
rs1643816	23432	178718682	A/C			
rs1650355	24007	178719257	A/C			
rs888763	26121	178721371	A/G	0.40	0.44	0.264
rs1862212	26273	178721523	A/T	0.56	0.53	0.529
rs1110514	26755	178722005	A/T	0.30	0.27	0.381
rs3797600	27411	178722661	C/T	0.55	0.54	0.840
rs3797602	27710	178722960	G/T	0.68	0.65	0.534
rs3797603	27842	178723092	C/T			
rs3776819	28379	178723629	C/T	0.45	0.47	0.662
rs252076	29603	178724853	C/T	0.46	0.46	0.986
rs252075	31232	178726482	C/G	0.36	0.34	0.666
rs252074	31504	178726754	A/G	0.35	0.33	0.604
rs252068	32583	178727833	C/G	0.47	0.48	0.648
rs252069	32794	178728044	A/G	0.27	0.26	0.640
rs194040	32840	178728090	C/T	0.31	0.30	0.734
rs252070	33044	178728294	C/T	0.61	0.55	0.157
rs3797606	33150	178728400	A/C	0.91	0.83	0.005
rs171667	33218	178728468	A/G	0.51	0.52	0.674
rs187539	33513	178728763	C/T	0.32	0.33	0.836
rs3836834	33959	178729209	- /TATCA AACTAC CATGAA A			
rs252071	34486	178729736	A/G	0.30	0.30	0.942
rs252072	36289	178731539	C/T	0.50	0.49	0.684
rs252073	36570	178731820	C/T			
rs379589	38247	178733497	A/T	0.60	0.61	0.981
rs2052472	38477	178733727	A/C	0.06	0.06	0.856
rs2052471	38518	178733768	C/T	0.91	0.86	0.079
rs2052470	38529	178733779	C/T	0.82	0.83	0.828
rs2052469	38667	178733917	A/G	0.82	0.82	0.983
rs3797608	39781	178735031	C/T	0.06	0.06	0.969
rs3797609	39856	178735106	C/T	0.05	0.05	0.879
rs3822601	39927	178735177	C/T	0.07	0.08	0.838
rs153131	40506	178735756	A/G	0.76	0.76	0.981
rs751546	41869	178737119	C/G	0.91	0.92	0.526
rs2279979	42452	178737702	C/T	0.92	0.92	0.906
rs252060	44788	178740038	C/T	0.81	0.85	0.157
rs3797610	46059	178741309	A/C	0.18	0.16	0.593
rs194039	46846	178742096	A/G	0.39	0.49	0.005
rs168773	47712	178742962	A/T	0.37	0.43	0.098
rs252061	48796	178744046	C/T	0.19	0.15	0.164
rs187537	49441	178744691	C/G			
rs252062	49602	178744852	A/T	0.93	0.95	0.290
rs2431255	49723	178744973	A/C	0.23	0.19	0.201
rs3797612	50050	178745300	C/T	0.32	0.38	0.102

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3797613	50171	178745421	C/T	0.23	NA	
rs614114	50477	178745727	C/T	0.48	0.51	0.423
rs252063	50818	178746068	C/T	0.60	0.51	0.011
rs252064	50833	178746083	C/T	0.51	0.56	0.265
rs252065	50881	178746131	A/G	0.22	0.18	0.175
rs450502	50882	178746132	A/G			
rs439252	51386	178746636	C/T			
rs252066	51534	178746784	C/T	0.18	0.16	0.451
rs457957	52317	178747567	A/G	0.67	0.68	0.728
rs3797614	52368	178747618	C/T			
rs423552	52970	178748220	A/G	0.89	0.91	0.398
rs398829	53023	178748273	A/G			
rs416646	53356	178748606	A/G	0.54	0.55	0.643
rs187450	53882	178749132	G/T			
rs337807	54553	178749803	C/T	0.49	0.59	0.009
rs337806	55475	178750725	A/C	0.11	0.10	0.889
rs1396438	55530	178750780	A/G	0.61	0.50	0.007
rs1396437	55691	178750941	C/T			
rs2411811	55848	178751098	A/C			
rs2898813	55879	178751129	C/G			
rs189256	56316	178751566	A/G	0.17	0.17	0.923
rs173072	56911	178752161	A/C			
rs337805	57320	178752570	A/G	0.27	0.25	0.582
rs191415	57391	178752641	C/T			
rs180045	57437	178752687	C/T	0.56	0.48	0.115
rs189255	57478	178752728	C/G	0.16	0.12	0.168
rs652766	57500	178752750	C/T	0.55	0.61	0.231
rs466750	59111	178754361	G/T	0.31	0.28	0.473
rs442406	59333	178754583	A/G	0.58	0.63	0.209
rs662407	59715	178754965	A/G	0.30	0.28	0.449
rs592971	59804	178755054	A/G			
rs457187	59851	178755101	A/G	0.23	0.21	0.402
rs459490	59929	178755179	C/T	0.20	0.19	0.708
rs459668	60052	178755302	C/T	0.21	0.20	0.821
rs462646	60240	178755490	C/T	0.44	0.41	0.460
rs458272	60359	178755609	G/T	0.22	0.20	0.524
rs463455	60381	178755631	A/G	0.23	0.22	0.629
rs675880	60456	178755706	C/T	0.65	0.67	0.564
rs810617	60724	178755974	C/G			
rs464156	60875	178756125	C/T	0.37	0.34	0.439
rs458083	60968	178756218	A/G			
rs467333	60978	178756228	C/G	0.11	0.11	0.902
rs465381	60998	178756248	C/T			
rs466363	61557	178756807	C/T	0.32	0.34	0.547
rs2457099	62091	178757341	C/T	0.43	0.43	0.974
rs463901	62645	178757895	C/T	0.39	0.43	0.342
rs465621	62943	178758193	A/C	0.59	0.64	0.195
rs463724	63131	178758381	A/T	0.09	0.07	0.539
rs465242	63145	178758395	G/T			
rs467419	63406	178758656	A/G	0.66	0.67	0.752
rs456135	63427	178758677	C/G	0.79	0.85	0.029
rs464536	63554	178758804	C/T	0.36	0.32	0.332
rs461898	63661	178758911	A/G	0.28	0.31	0.423
rs389558	64093	178759343	A/G	0.20	0.23	0.311
rs466752	64153	178759403	C/T	0.36	0.35	0.781
rs455655	64409	178759659	C/G	NA	0.72	NA
rs463435	64544	178759794	C/T	0.72	0.68	0.230
rs2174971	65257	178760507	C/T	0.56	0.51	0.142
rs1979979	65626	178760876	A/G	0.05	0.05	0.993
rs411804	65739	178760989	A/G	0.80	0.77	0.343
rs1623885	66392	178761642	C/T	0.84	0.84	0.819
rs1643811	66720	178761970	C/T	0.22	0.23	0.847
rs434430	69177	178764427	A/T			
rs187538	69336	178764586	G/T			

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs252067	69636	178764886	A/G	0.21	0.24	0.369
rs459319	69823	178765073	A/G	0.18	0.15	0.353
rs467289	69928	178765178	C/T	0.27	0.22	0.179
rs462644	70547	178765797	C/T	0.60	0.61	0.609
rs458752	70633	178765883	C/T	0.18	0.15	0.271
rs708320	71805	178767055	A/C			
rs457954	72181	178767431	C/G	0.72	0.72	0.882
rs24 11810	72200	178767450	C/T	0.29	0.30	0.630
rs3084687	72474	178767724	-A/T	0.13	0.11	0.509
rs69638	72567	178767817	C/G	0.54	0.57	0.440
rs455452	72973	178768223	A/G	0.60	0.58	0.499
rs464850	73468	178768718	A/G	0.10	0.09	0.839
rs431472	73889	178769139	A/G	0.35	0.27	0.025
rs24 11809	75730	178770980	C/T			
rs24 57094	75970	178771220	A/G	0.71	0.70	0.792
rs24 57095	76114	178771364	A/G	0.75	0.76	0.602
rs2261740	76342	178771592	C/T	0.36	0.36	0.924
rs11 09180	76449	178771699	A/G			
rs11 09179	76465	178771715	C/T			
rs11 09178	76791	178772041	A/C	0.45	0.42	0.420
rs456909	78042	178773292	A/G	0.53	0.51	0.598
rs469124	80758	178776008	A/G			
rs468039	80778	178776028	C/T			
rs467017	81356	178776606	A/C	0.34	0.35	0.762
rs469290	81576	178776826	A/G	0.49	0.44	0.223
rs469090	81689	178776939	C/T	0.83	0.84	0.883
rs469568	81759	178777009	G/T	0.36	0.30	0.115
rs468386	81950	178777200	C/G			
rs469349	82562	178777812	A/C			
rs469099	83591	178778841	C/T	0.65	0.67	0.560
rs456868	83700	178778950	A/G			
rs465389	83821	178779071	C/G			
rs463892	83842	178779092	C/G			
rs468548	83923	178779173	G/T			
rs654612	83929	178779179	A/C			
rs468542	84021	178779271	C/G			
rs469262	84175	178779425	C/T	0.45	0.43	0.762
rs708323	84417	178779667	A/G	0.74	0.74	0.899
rs469089	84747	178779997	C/G			
rs469396	85746	178780996	C/G	0.39	0.42	0.569
rs468723	86129	178781379	C/T	0.36	0.34	0.573
rs467604	86335	178781585	A/G	0.35	0.36	0.763
rs338874	87315	178782565	C/G	0.42	0.40	0.564
rs338875	87648	178782898	A/G	0.46	0.45	0.701
rs1385803	87764	178783014	A/C			
rs1385804	87770	178783020	C/G			
rs338876	88221	178783471	C/T	0.41	0.44	0.580
rs189803	90474	178785724	A/C			
rs452215	91148	178786398	G/T			
rs641170	91150	178786400	G/T			
rs584398	91160	178786410	G/T			
rs385330	91733	178786983	C/T			
rs429538	91772	178787022	A/C			
rs371229	91785	178787035	C/T			
rs460874	93140	178788390	A/T	0.73	0.75	0.550
rs646121	93148	178788398	A/T	0.93	0.92	0.697
rs468262	96080	178791330	A/G			
rs467863	96157	178791407	C/G			
rs191434	96313	178791563	A/C			
rs2054782	96759	178792009	C/T	0.43	0.40	0.473
rs468499	97026	178792276	A/C			
rs180287	97320	178792570	C/G			
rs338877	97732	178792982	A/T	0.04	0.04	0.928
rs650665	98713	178793963	C/G			

dbSNP rs#	Position in SEQ ID NO: 6	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs 193419	99707	178794957	A/C			
rs 180288	99959	178795209	C/G			
rs 186834	100009	178795259	A/G			
rs 189266	100020	178795270	C/G			
rs 189267	100065	178795315	A/C			
rs 170937	100086	178795336	C/G			
rs 463263	101270	178796520	C/G			
rs 463262	101276	178796526	G/T			
rs 460454	101371	178796621	C/T			
rs 460455	101376	178796626	C/G			
rs 460505	101439	178796689	C/T			
rs 931316	101820	178797070	C/T			
rs 463431	102392	178797642	C/G			
rs 461542	102602	178797852	A/G			
rs 463557	102604	178797854	A/C			
rs 191453	102896	178798146	C/T	0.06	0.06	0.929
rs 2271212	189104	178884354	C/T	0.66	0.56	0.012
rs 462009	189134	178884384	C/T			
rs 2271211	189205	178884455	A/G			
rs 396474	Not mapped	Not mapped	A/C			
rs 428901	Not mapped	Not mapped	A/T	0.61	0.72	0.002
rs 452300	Not mapped	Not mapped	G/T			
rs 670256	Not mapped	Not mapped	G/T			

[0286] Allelotyping results were considered particularly significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The allelotyping p-values were plotted in Figure 1E for the discovery cohort. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figure 1E can be determined by consulting Table 35. For example, the left-most X on the left graph is at position 17 8695460. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0287] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The generally bottom-most curve is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0288] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is placed at the 3' end of each gene to show the direction of transcription.

Example 9

BVES Proximal SNPs

[0289] It was discovered that rs 1018810, an intronic SNP in the *BVES* gene, is associated with occurrence of osteoarthritis in subjects. *BVES* was identified as a blood vessel epicardial substance. Sequence analysis predicted 3 transmembrane helices with an extracellular C terminus. Northern blot analysis revealed that expression of an approximately 5.5-kb *BVES* transcript is restricted to skeletal muscle and adult and fetal heart. *BVES* is highly expressed in osteoarthritic cartilage according to EST database analysis, and may play a role in chondrocyte and/or bone cell development. *BVES* biological activity may be modulated by addition of an antibody, a recombinant binding partner, a binding agent, or a recombinant *BVES* protein or functional fragment thereof.

[0290] One hundred fifty-four additional allelic variants proximal to rs 1018810 were identified and subsequently allelotyped in osteoarthritis case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 38. The chromosome positions provided in column four of Table 38 are based on Genome "Build 34" of NCBI's GenBank.

TABLE 38

dbSNP rs#	Chromosome	Position in SEQ ID NO: 7	Chromosome Position	Allele Variants
rs2400080	6	241	105557091	A/G
rs6930209	6	801	105557651	A/G
rs221628	6	899	105557749	A/G
rs221629	6	2091	105558941	C/G
rs221630	6	2290	105559140	C/T
rs221631	6	2440	105559290	A/G
rs1149284	6	4959	105561809	G/T
rs221633	6	7914	105564764	C/G
rs423366	6	7969	105564819	A/G
rs436460	6	7972	105564822	C/T
rs2211010	6	10831	105567681	C/T
rs379908	6	12399	105569249	C/T
rs1149285	6	13841	105570691	C/T
rs7341194	6	14461	105571311	C/T
rs715153	6	14680	105571530	C/T
rs221634	6	16808	105573658	A/T
rs7757307	6	18231	105575081	C/T
rs221635	6	18394	105575244	C/T
rs4145418	6	18505	105575355	G/T
rs221636	6	18684	105575534	A/T
rs3185958	6	19257	105576107	C/T
rs4946654	6	20263	105577113	A/T

dbSNP rs#	Chromosome	Position in SEQ ID NO: 7	Chromosome Position	Allele Variants
rs221637	6	20656	105577506	A/C
rs221638	6	21499	105578349	A/G
rs221639	6	21563	105578413	A/C
rs643545	6	21612	105578462	C/G
rs221640	6	21834	105578684	C/T
rs3957696	6	22406	105579256	A/T
rs3995554	6	22408	105579258	A/T
rs7453502	6	22685	105579535	A/T
rs1190471	6	23303	105580153	C/T
rs221641	6	23306	105580156	C/G
rs221642	6	25139	105581989	A/G
rs1190472	6	25211	105582061	C/T
rs1190473	6	25364	105582214	A/G
rs186404	6	25381	105582231	A/C
rs221643	6	25414	105582264	A/T
rs221644	6	25835	105582685	C/T
rs1203475	6	26214	105583064	A/G
rs221645	6	27224	105584074	A/G
rs170277	6	27526	105584376	A/G
rs221646	6	27934	105584784	C/T
rs221647	6	28550	105585400	C/T
rs221648	6	29015	105585865	A/G
rs221649	6	29879	105586729	G/T
rs221650	6	29979	105586829	A/G
rs1149287	6	30030	105586880	A/G
rs221651	6	30585	105587435	C/T
rs7762591	6	31753	105588603	C/G
rs7748555	6	31934	105588784	C/T
rs5878833	6	33227	105590077	-T
rs5878834	6	33228	105590078	-T
rs221652	6	35172	105592022	C/T
rs221653	6	36901	105593751	A/G
rs221654	6	36921	105593771	A/G
rs221655	6	36932	105593782	A/G
rs221656	6	37061	105593911	C/T
rs221657	6	37570	105594420	C/T
rs221658	6	38745	105595595	G/T
rs110065	6	38970	105595820	A/T
rs221659	6	39725	105596575	C/T
rs221660	6	40070	105596920	A/C
rs7742821	6	40460	105597310	C/G
rs221662	6	41470	105598320	A/G
rs7748426	6	41562	105598412	A/G
rs6911494	6	41956	105598806	A/G
rs6939846	6	42047	105598897	A/T
rs368471	6	42280	105599130	A/G
rs430190	6	42358	105599208	A/G
rs455114	6	42629	105599479	C/G
rs405956	6	43075	105599925	C/T
rs5878835	6	43387	105600237	-A
rs1473814	6	43393	105600243	G/T
rs423272	6	43438	105600288	C/T

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 7	Chromosome Position	Allele Variants
rs413806	6	44115	105600965	A/G
rs4946655	6	44537	105601387	A/G
rs6915632	6	45642	105602492	A/G
rs2095723	6	46629	105603479	A/G
rs7450078	6	47496	105604346	A/G
rs7453071	6	47515	105604365	A/C
rs1018810	6	48329	105605179	A/G
rs7450944	6	48862	105605712	C/G
rs7748657	6	48908	105605758	A/G
rs1013137	6	49038	105605888	C/T
rs5878836	6	49080	105605930	-/T
rs1981480	6	50204	105607054	A/T
rs1981479	6	50404	105607254	A/G
rs3035187	6	50426	105607276	-/TTA
rs7453993	6	50531	105607381	C/T
rs2001119	6	50840	105607690	C/T
rs2001118	6	50964	105607814	C/T
rs2001117	6	50971	105607821	C/T
rs6940433	6	51378	105608228	C/T
rs1318746	6	52610	105609460	A/C
rs763099	6	53906	105610756	A/T
rs5878837	6	53951	105610801	-/C
rs964731	6	54111	105610961	A/C
rs964730	6	54149	105610999	G/T
rs6921869	6	55563	105612413	C/G
rs3945029	6	55999	105612849	C/T
rs4945715	6	58415	105615265	C/G
rs7775252	6	58961	105615811	C/G
rs7742098	6	60447	105617297	C/T
rs3757289	6	61377	105618227	A/G
rs6905458	6	61528	105618378	A/G
rs3757290	6	61606	105618456	C/G
rs2275289	6	62140	105618990	A/G
rs4945716	6	62461	105619311	C/T
rs6922638	6	63826	105620676	C/T
rs7739572	6	64950	105621800	G/T
rs6901187	6	65076	105621926	G/T
rs4946656	6	66121	105622971	C/T
rs1338020	6	66406	105623256	C/T
rs7771472	6	67051	105623901	A/C
rs6926260	6	68860	105625710	C/T
rs6926627	6	69014	105625864	C/T
rs4946657	6	70796	105627646	C/T
rs6571218	6	72325	105629175	G/T
rs7449944	6	73414	105630264	A/C
rs952175	6	75258	105632108	C/G
rs1890228	6	76347	105633197	A/G
rs1933237	6	76839	105633689	A/C
rs1338019	6	77358	105634208	A/G
rs7453127	6	77822	105634672	A/G
rs7381551	6	77946	105634796	G/T
rs6571219	6	80002	105636852	A/G

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 7	Chromosome Position	Allele Variants
rs6571220	6	80024	105636874	A/G
rs2185017	6	80285	105637135	A/G
rs1591720	6	80397	105637247	C/G
rs6925046	6	82075	105638925	C/T
rs6940423	6	82153	105639003	A/G
rs1190274	6	83981	105640831	A/G
rs1190276	6	84184	105641034	A/G
rs1591719	6	85089	105641939	C/T
rs1933236	6	85288	105642138	A/G
rs6905202	6	85330	105642180	C/T
rs1209150	6	85581	105642431	A/T
rs1190277	6	85642	105642492	A/G
rs6926278	6	86433	105643283	A/G
rs1190278	6	86904	105643754	A/G
rs4626463	6	88391	105645241	A/G
rs6924620	6	89042	105645892	C/T
rs1190280	6	90828	105647678	G/T
rs4557552	6	92676	105649526	C/T
rs6932711	6	92881	105649731	C/T
rs1686140	6	94227	105651077	G/T
rs1190281	6	94585	105651435	A/G
rs2308162	6	94616	105651466	-/ATAA
rs1190282	6	94712	105651562	C/G
rs1765907	6	94738	105651588	A/G
rs5878838	6	95253	105652103	-/G
rs1190283	6	95522	105652372	A/G
rs1190284	6	95869	105652719	G/T
rs1190285	6	97856	105654706	C/T

Assay for Verifying and Allelotyping SNPs

[0291] The methods used to verify and allelotype the 154 proximal SNPs of Table 38 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 39 and Table 40, respectively.

TABLE 39

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs2400080	ACGTTGGATGGTGCCCAGCAAGTGATGATA	ACGTTGGATGACAGAGCAAGACTCCATCTC
rs6930209	ACGTTGGATGGCTCTGTGGTGCAATTTAC	ACGTTGGATGGGTTCTCTCACTTAACTGTG
rs221628	ACGTTGGATGAGTGAGAGAAACAAATGTTG	ACGTTGGATGCCAGTTTGGCTTCATTTGC
rs221629	ACGTTGGATGTCTGTCCATTTCTCCCTCTG	ACGTTGGATGGCTGATTCTTGGCAAAAGGC
rs221630	ACGTTGGATGTCCTTCTCATTGCTGTGTAG	ACGTTGGATGTCATGTGCAAGAGCCAAAAG
rs221631	ACGTTGGATGCACTGGCCCTCTATAAATGC	ACGTTGGATGCCAGCCCCCTGCATTATTAT
rs1149284	ACGTTGGATGGATGAGAAATTAAGTAGACAC	ACGTTGGATGGTCCATTTGGTTTTCATTTG
rs221633	ACGTTGGATGCTTAACAATTTGTCTTGGAG	ACGTTGGATGAGCCACATATACCAAAAAAC
rs423366	ACGTTGGATGAGCCACATATACCAAAAAAC	ACGTTGGATGGAGATCTTTGCATGTCAATAC
rs436460	ACGTTGGATGAGCCACATATACCAAAAAAC	ACGTTGGATGGAGATCTTTGCATGTCAATAC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs2211010	ACGTTGGATGTTTTTGTAGACAGAGTCTCG	ACGTTGGATGTTTGCAGTGAGCTGAGATTG
rs379908	ACGTTGGATGTGAGTGGGCAAAATGGTTCC	ACGTTGGATGCTCTCCTGCAGACACATCAA
rs1149285	ACGTTGGATGCCAAATACATTTATGACTCC	ACGTTGGATGGAGAGAGATTCCATCTCAAA
rs7341194	ACGTTGGATGCTGTAGAAACCAGCTAAACTG	ACGTTGGATGCTGACTAGACTCTGACTTTC
rs715153	ACGTTGGATGTTTTGTTGAATATTCGCTGC	ACGTTGGATGCTTCCATATAGAAAGGATTCC
rs221634	ACGTTGGATGTGCCATAACATCTAGAGCC	ACGTTGGATGTTGGTCTCTGTAGGTTTCGG
rs7757307	ACGTTGGATGTGCTTAAGTTGAACAGTGCC	ACGTTGGATGGCAAAGTCTCCAAACATTTC
rs221635	ACGTTGGATGGGCAGCACAGACAGTAAATG	ACGTTGGATGTGCAGGTATTCTAGCTAGGC
rs4145418	ACGTTGGATGTGCATTGCCAGTCTCTTAGC	ACGTTGGATGGGCCTTCTAGTGAAGACTAG
rs221636		
rs3185958	ACGTTGGATGGACACAGATCATACAACCAC	ACGTTGGATGAGCATCAAACCTCTGTCTTAC
rs4946654	ACGTTGGATGATGTAGTCAGAAGAGTGGTC	ACGTTGGATGGGTACTGATAAAATTTGCC
rs221637	ACGTTGGATGCAATCGTAGCTTACTGTGGG	ACGTTGGATGCTGTAGTCCAGCTACTCAAG
rs221638	ACGTTGGATGCACACCTGGCTGAAAATCTTA	ACGTTGGATGTGGTTATTTCTAGGCGATGG
rs221639	ACGTTGGATGCCCGCATGTGTATGTATCTC	ACGTTGGATGCCCATCGCCTAGAAATAACC
rs643545	ACGTTGGATGAAAATCACCCGCATGTGTAT	ACGTTGGATGCGCCTAGAAATAACCATTAGC
rs221640	ACGTTGGATGTAATCCCAGCACTTTGGGAG	ACGTTGGATGTTTCACCATGTTAGCCAGGC
rs3957696	ACGTTGGATGAACCAAGTATGTTGCCCTTTC	ACGTTGGATGCCAGGCAGTCCAAATTAATTC
rs3995554	ACGTTGGATGAACCAAGTATGTTGCCCTTTC	ACGTTGGATGCCAGGCAGTCCAAATTAATTC
rs7453502	ACGTTGGATGCTCCAAGGTTGGAGTTTGTG	ACGTTGGATGTTTCTGAGCTCCTCAGCATC
rs1190471	ACGTTGGATGATATGTGGCCCGATGATCTC	ACGTTGGATGCCTCCCAAAGTGCTAGGATT
rs221641	ACGTTGGATGCCTCCCAAAGTGCTAGGATT	ACGTTGGATGATATGTGGCCCGATGATCTC
rs221642	ACGTTGGATGTCTTCCACCATGATTGTGAG	ACGTTGGATGAGACATACCTGAGACTGGAC
rs1190472	ACGTTGGATGTGTCCAGTCTCAGGTATGTC	ACGTTGGATGGCCCAGCTAAGGTTTTGTAG
rs1190473	ACGTTGGATGTTGATCACACCACTGCACTC	ACGTTGGATGCCCCAATGAAGAAGTCTTGC
rs186404	ACGTTGGATGTTGATCACACCACTGCACTC	ACGTTGGATGCCCCAATGAAGAAGTCTTGC
rs221643	ACGTTGGATGCCCCAATGAAGAAGTCTTGC	ACGTTGGATGGAGACACAGTGAGACTGTCA
rs221644	ACGTTGGATGGTGTCTTTCTAGCTAGCTC	ACGTTGGATGTTACAGATGGGTTCCAGGGAG
rs1203475	ACGTTGGATGTAATCCCAGCTACTTGGGAG	ACGTTGGATGACAATCTCGGCTCACTGCAA
rs221645	ACGTTGGATGTGTTTTTCATCTGCCAATG	ACGTTGGATGGCTGCTGTTAAGGACCACAT
rs170277	ACGTTGGATGACAAGGAAGTTCTGAACCTC	ACGTTGGATGTTTTGGATCAAGAGGTGACC
rs221646	ACGTTGGATGAATTGGCTCTTCTCTCTGCC	ACGTTGGATGTTACAGCAGAAATGGCTGGA
rs221647	ACGTTGGATGTTCCAGCTCCTTTCTCTTAG	ACGTTGGATGTTCTTAAGAAAATGCCCTC
rs221648	ACGTTGGATGATCATGCCACTGCACTCCAG	ACGTTGGATGTTAGGTCTCCAGGACGACAG
rs221649	ACGTTGGATGGACAGGATGAAGAAGAAGGC	ACGTTGGATGTCTTGCTATTGCGCAAGGAC
rs221650	ACGTTGGATGTAATATCCAGGATCCAGCTG	ACGTTGGATGTTGAACCCCTGAACTCAAGC
rs1149287	ACGTTGGATGATGGAGGTCTCACCATTGTT	ACGTTGGATGTAGCACTTTGGGAGGCCAAG
rs221651	ACGTTGGATGGGAGGATCACTTGAATCCAG	ACGTTGGATGAGACAGGTTCTTGCTCTGTT
rs7762591	ACGTTGGATGATCTCTGCTCACTGCAGCTT	ACGTTGGATGAAATTAGCCAGGTGTGGTGG
rs7748555	ACGTTGGATGTTGGGATTACAGGTGTGAGC	ACGTTGGATGCCCACTGCTTCACTTGACTA
rs5878833	ACGTTGGATGACACTGTCTACACTGCCTTC	ACGTTGGATGACCTGACTTCAAAGGTCCTG
rs5878834	ACGTTGGATGACACTGTCTACACTGCCTTC	ACGTTGGATGACCTGACTTCAAAGGTCCTG
rs221652	ACGTTGGATGTACTTTCTACTCAGGGAAGG	ACGTTGGATGAGTTTACACGCGCATAAGAC
rs221653	ACGTTGGATGGTTTCACTGTGTTAGCCAGG	ACGTTGGATGTAATCCCAGCACTCTGGGAG
rs221654	ACGTTGGATGGAGATCAAGACCATCCTGGC	ACGTTGGATGAGTAGCTGGGACTACAGGCA
rs221655	ACGTTGGATGGTCAGGAGATCAAGACCATC	ACGTTGGATGCCGCGCCCAGCTAATTTTTT
rs221656	ACGTTGGATGAGATGGAGTTTCACTCTGTC	ACGTTGGATGAATCCAGGAGGTGGAGTTTG
rs221657	ACGTTGGATGAGAACTCTTCCATCCTTGAC	ACGTTGGATGTTCTGCTTTAGTGCATCCAG
rs221658	ACGTTGGATGCCAGCTGAGTTCAAGCATTTG	ACGTTGGATGACACCCATATCTTCGCTACC
rs110065	ACGTTGGATGTGACATGCTCATAGCCCTTG	ACGTTGGATGAGATCAGCTGTCATTCACTG
rs221659	ACGTTGGATGCCAAACACAACCTCTACTTC	ACGTTGGATGCAGGTAAGGAAATTAAGGCAC
rs221660	ACGTTGGATGAATATGATGGAACACAGGGC	ACGTTGGATGTCTTAGCTCTCTTGAGTGTG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs7742821	ACGTTGGATGAGCTCTTGGGAAGTTCTCAC	ACGTTGGATGCCCCAACTCTCTCACCTATAC
rs221662	ACGTTGGATGGACAAATGGGTAAATGTTGGG	ACGTTGGATGAAGTGCTTTGAGTTTCTGAG
rs7748426	ACGTTGGATGATTACCCCTCACCACATCTG	ACGTTGGATGCCACCCCTCTCTGTTTCTT
rs6911494	ACGTTGGATGTCAATGGTACAGAAGGCCAG	ACGTTGGATGAACCCCTCGCTTGAATTAG
rs6939846	ACGTTGGATGTCCTCAAAGCTGGGCTTTCT	ACGTTGGATGAGACAAAAGGATCACCTGCC
rs368471	ACGTTGGATGCCCCAATACATCCAAAACC	ACGTTGGATGACCAGGCAAACCTGTAGAAG
rs430190	ACGTTGGATGTCTCTGGAAGATAGTTGGGC	ACGTTGGATGACTTCTACAGGTTTGCCTGG
rs455114	ACGTTGGATGCCCAGAAAATTGATTCTTAG	ACGTTGGATGACAGAAGTCTTTTCTGATC
rs405956	ACGTTGGATGAACTCCAAGTCAAGGACCC	ACGTTGGATGAAAGGTGTCCACTGTTTCGC
rs5878835	ACGTTGGATGCTGTCTTCCAGAGTCTTGAG	ACGTTGGATGTACATCCACTATGTACCCAC
rs1473814	ACGTTGGATGGTTAAAGAACCACAGAAGGC	ACGTTGGATGTACATCCACTATGTACCCAC
rs423272	ACGTTGGATGCACAGAAGGCCTTAAAAACC	ACGTTGGATGTCACGTTGCATTCTGTATC
rs413806	ACGTTGGATGCTGACAGATTTACATCGTG	ACGTTGGATGTTCCAGAGGATGAACAAAC
rs4946655	ACGTTGGATGCTAAAGAGTAGCTTTGGCTTG	ACGTTGGATGTTTTGTACGCTTTGCCTGAG
rs6915632	ACGTTGGATGGTCGTGATCTTGACTCACTG	ACGTTGGATGGCCTGTAATCCAGTTACTC
rs2095723	ACGTTGGATGTGTGCTCTCTCATGCCAGTA	ACGTTGGATGCTGTATAAAATACCTTCAGG
rs7450078	ACGTTGGATGGCCATCACCTCCAGATAATT	ACGTTGGATGAAGGCAGGAGGATCTCTTGA
rs7453071	ACGTTGGATGAATCCCAGCACTTTGGGAGG	ACGTTGGATGTATGTTGCCAGGCTCGTCT
rs1018810	ACGTTGGATGTGCTGCTCCCATTTCATG	ACGTTGGATGAAGGAGTAGAGACCTTGCTG
rs7450944	ACGTTGGATGATTACGCCACTACACCTCAG	ACGTTGGATGTTGTTCTACAGGACAAACC
rs7748657	ACGTTGGATGAGAGAGAGATGGAAGGGAG	ACGTTGGATGTCGAATCACGATCTGAACAG
rs1013137	ACGTTGGATGATTACAAGCAGTGTCACTCC	ACGTTGGATGGGTTAATGAATAGGTGGAAC
rs5878836	ACGTTGGATGTTGGTATGGAGTGACACTG	ACGTTGGATGCCAATGATAATCTCCAGTGTC
rs1981480	ACGTTGGATGCGACTGTCTTCTTCTGCAAG	ACGTTGGATGTGCTGCACTTCCCTACTCTT
rs1981479	ACGTTGGATGTGAGTAGCTAGAACTACAGG	ACGTTGGATGATCACTGCAGCCTTAAACTC
rs3035187	ACGTTGGATGTGAGTAGCTAGAACTACAGG	ACGTTGGATGATCACTGCAGCCTTAAACTC
rs7453993	ACGTTGGATGTGACAAAGTGAGACCAACTC	ACGTTGGATGTGGGAGATCACCTTTCATAC
rs2001119	ACGTTGGATGGCTTCTTTAGGCTTTCATTTT	ACGTTGGATGTGAGTTTGTGTTAAAGGCTC
rs2001118	ACGTTGGATGGGTCCAGCCAAAAACAACC	ACGTTGGATGAGGCTGGAATTTACAAGGCC
rs2001117	ACGTTGGATGGTCCAGCCAAAAACAACCC	ACGTTGGATGAGGCTGGAATTTACAAGGCC
rs6940433	ACGTTGGATGTTGTGAGCTACCTCATTAC	ACGTTGGATGCAACATCTGGGTATTTGTG
rs1318746	ACGTTGGATGTAAGCTGGTGCTTATTTTACAG	ACGTTGGATGGGTGGCCATAAACAATAAGC
rs763099	ACGTTGGATGGAGGCAAGTTGTGAAAGACC	ACGTTGGATGGGCCCTTGAAGTTTCTCAG
rs5878837	ACGTTGGATGTACCAGCCGTATTCATCAG	ACGTTGGATGTGAAAGACCTTCTGCCCATC
rs964731	ACGTTGGATGGGAAATCATACCCCTTTTCC	ACGTTGGATGTGAGGGATACTTGAGCTCTG
rs964730	ACGTTGGATGCACTCTGGCAAAGGGATTTA	ACGTTGGATGGTAGGAAAGCAGAAAGGTAC
rs6921869	ACGTTGGATGTAGTAGAGACAGGGTTTAC	ACGTTGGATGTACTTGGGAGGCTAAGATGG
rs3945029	ACGTTGGATGCTCTTCTGTAAATCTTGCC	ACGTTGGATGAGAGAAAGGCTGAACACATG
rs4945715	ACGTTGGATGCTCAAGGGACAGTCATTGAG	ACGTTGGATGGTCAGGGTGCTCATGAATTG
rs7775252	ACGTTGGATGGACTAGGGATTGGATTTTGG	ACGTTGGATGTTTCTTATCCAGCTATGGC
rs7742098	ACGTTGGATGGAAGAAAACCAGAAAACCTGGC	ACGTTGGATGAAGAACTTCGTTCTTTCCCC
rs3757289	ACGTTGGATGGCGATTTTATTTTGTAGTACAG	ACGTTGGATGAATACTTGTGCCTCAAGAAG
rs6905458	ACGTTGGATGAGGAATATCAGCCTTTTGGG	ACGTTGGATGGCTCTTCTAACAGAAGTGACC
rs3757290	ACGTTGGATGTAACAATGCCAGCACAACAG	ACGTTGGATGTGCTCCAGAGTTAATTTGTC
rs2275289	ACGTTGGATGTTGAAAAGGAACTCAGTGGC	ACGTTGGATGTGCCAGTTAGTCTTCTGAAC
rs4945716	ACGTTGGATGTAGAGCCTCACTGTGTTACC	ACGTTGGATGAATTCTGGCACTTTGGGAGG
rs6922638	ACGTTGGATGGCTTAGTGTCTGTGCTTTTG	ACGTTGGATGCCTGCTGTTTCATTTGAGG
rs7739572	ACGTTGGATGGTTTTAAGAGACATTGGGTG	ACGTTGGATGTCTATTTGGACCATGCATT
rs6901187	ACGTTGGATGTCAGCACAGACCCCTTAAATG	ACGTTGGATGGGCTTTTTTCTCACCCACC
rs4946656	ACGTTGGATGTGGCCCAGACGATATAAAGG	ACGTTGGATGATTAAGCTCCCCACTTAGGC
rs1338020	ACGTTGGATGTCTGTGGTCAACAACAGTCC	ACGTTGGATGCATCTCAGGCAGGATATAGC
rs7771472	ACGTTGGATGTTACCTGAAGGTGAATCTAG	ACGTTGGATGGTACAAAACCTTTGGAAAAC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs6926260	ACGTTGGATGTACCACAGTGCTGGGATTAC	ACGTTGGATGCGTAGAGTAGTGCAATTGTGC
rs6926627	ACGTTGGATGAGGTGTGCACCCATTATCCA	ACGTTGGATGGGATACTATACCCATTTACTC
rs4946657	ACGTTGGATGCCAGGTAGAATTATTATGGG	ACGTTGGATGCCACCATTAAATCACTGTATC
rs6571218	ACGTTGGATGCGCACGACACCTTATTAAG	ACGTTGGATGTTGACAATAGGTAAGTGGC
rs7449944	ACGTTGGATGAACTTTGTGCGGCCCTGGCGG	ACGTTGGATGCCAGCGAGGAGGGACAGAG
rs952175	ACGTTGGATGATGCTCTGCCAGCCTTTTTT	ACGTTGGATGTCAAACAGCTGGTAGGGAC
rs1890228	ACGTTGGATGTTAAGGCATTCCCATATCCT	ACGTTGGATGCCAGATGTATGAATAGTAGC
rs1933237	ACGTTGGATGGGGTTCAAGCAATTCCTGTC	ACGTTGGATGCAAAATTAGCCCGGTGTGG
rs1338019	ACGTTGGATGTATGTGTGTCACAAAGGGAG	ACGTTGGATGCCTGCAGAACTACAAACATG
rs7453127	ACGTTGGATGCATCACCTCAGATAGTTACC	ACGTTGGATGGTGACTCCAGTTAGCTATAC
rs7381551	ACGTTGGATGAGTTTGTACCTTTGACCAC	ACGTTGGATGGTTGAACACAGAAACAGAG
rs6571219	ACGTTGGATGGACAGTACTGAAAGTCTTCG	ACGTTGGATGCTTCTTCTATCTGATTTGG
rs6571220	ACGTTGGATGTCTATCTGATTTGGAAGGC	ACGTTGGATGAACAAGACGAGAGTGTCTTG
rs2185017	ACGTTGGATGATGTGGGAAGATCACTTGAG	ACGTTGGATGAGCCCGCTAATTGTCTAT
rs1591720	ACGTTGGATGTTGGAATTACAGGTGTGAGC	ACGTTGGATGACAAAGCCACAGCTAACATC
rs6925046	ACGTTGGATGGCTTGCTTTTTGAGACAGGG	ACGTTGGATGTAGAGGCTGTAGTGAGCTGT
rs6940423	ACGTTGGATGGTGCTGGGATTACAGATGTG	ACGTTGGATGCCCTGTCTCAAAAAGCAAGC
rs1190274	ACGTTGGATGCATTTAGTCTCTGAGGACAAC	ACGTTGGATGCCTTTCTAACCCTAAATACC
rs1190276	ACGTTGGATGCTGTAATCCCAGCACTTTGG	ACGTTGGATGTAGTAGAGACTGGCTTTCAC
rs1591719	ACGTTGGATGCTCACACATTCCTGAAAG	ACGTTGGATGCTGTGAGAACTGCTCTGTC
rs1933236	ACGTTGGATGCCAAGTCATTTGAAACCTTC	ACGTTGGATGTAAGCTCAGAAAATGGCATC
rs6905202	ACGTTGGATGGTATTACAGTGTGAATCAGG	ACGTTGGATGCCCAATTCAACATCAATTTTC
rs1209150	ACGTTGGATGTCCTCCAGAACTTTTGACC	ACGTTGGATGGGCCTTTATTACTTGCTACC
rs1190277	ACGTTGGATGATCATGTGCTAAGCACCACG	ACGTTGGATGCCCTCCAGGTCAAAAGTTTC
rs6926278	ACGTTGGATGTAGAACTCCCAGGCTCAAGA	ACGTTGGATGATTAGCTGGGTGTAGTGGC
rs1190278	ACGTTGGATGAGATACTGAGAAGGGTAGTC	ACGTTGGATGGTGC TACTGAATACTAGATC
rs4626463	ACGTTGGATGAGAAATTGCCAACCAGCCTC	ACGTTGGATGGGTCCAGAAAGCAAGCAAAG
rs6924620	ACGTTGGATGAGAAACAATGCCTGGCACATG	ACGTTGGATGTGACAGAGTGAGACTCTGTC
rs1190280	ACGTTGGATGTAGAAAGTGCCATCCAATGC	ACGTTGGATGACAACTAGGCAGACAGTAC
rs4557552	ACGTTGGATGCGTCCTTTACATAACCCAG	ACGTTGGATGCATTCTCTCGGTGACCTAGG
rs6932711	ACGTTGGATGATCACCTGCTCAAGGTCATC	ACGTTGGATGGATGGTGCAATTTGCATGCAG
rs1686140	ACGTTGGATGAGAAAGAACCCTAGTTGGAG	ACGTTGGATGGAACATAGTCTGCATGTGATC
rs1190281	ACGTTGGATGCACTTTTTTGCTACAACCTC	ACGTTGGATGATCTCTTGCAATTTATTCTAC
rs2308162	ACGTTGGATGCACTTTTTGCTACAACCTCC	ACGTTGGATGGCATCAAGTAAGTGCACATT
rs1190282	ACGTTGGATGTATGTGGACAGTAGCAACCC	ACGTTGGATGAGATCAGGAGTTGCTTCTC
rs1765907	ACGTTGGATGCTTCTTGAGAAGCAACTCC	ACGTTGGATGGGGAAGATGAAATCCACTT
rs5878838	ACGTTGGATGCCCTGTCATTCAAGGCATAG	ACGTTGGATGTTGCTCAGCATCGCTACATC
rs1190283	ACGTTGGATGCCCACTGACCTACAATATAT	ACGTTGGATGGACAAGATTGAAGATGGCTAG
rs1190284	ACGTTGGATGATCTTCAAACTGCCAGAC	ACGTTGGATGGCCAGTGGATTTCAGTTGTT
rs1190285	ACGTTGGATGACTTGAGTCACAGACATAGC	ACGTTGGATGGGCTCTTGATTATTTCTGC

TABLE 40

dbSNP rs#	Extend Primer	Term Mix
rs2400080	TCCTTTACTTTACCTTTTTTCC	ACG
rs6930209	GATTTTTATGCAAATATCAGATGA	ACT
rs221628	AAGAATAGACATATTTGTAGATCA	ACT
rs221629	TCTCCCTCTGGCCCAACTG	ACT
rs221630	GACAGGTGATGGCTTGGA	ACG

dbSNP rs#	Extend Primer	Term Mix
rs221631	TGTCAAAATGGAAGATGATTAAT	ACT
rs1149284	CTAGACACATTGTCTGCTAGT	ACT
rs221633	AACAATTTGTCTTGGAGATCTTT	ACT
rs423366	ACCAAAAAACATTTTGCAGATAG	ACG
rs436460	ATATACCAAAAAACATTTTGCAGA	ACG
rs2211010	GAGACAGAGTCTCGCTCTGT	ACG
rs379908	TGGATAACACAGTGCATACCA	ACG
rs1149285	ATTTATGAAGCACAAAGAACAAC	ACT
rs7341194	ACTGGAAAAATTTTTTCCTTTGT	ACT
rs715153	GCCCTCTAGTGGGCTTAATG	ACT
rs221634	GCCAGGATGACCCCAAATA	CGT
rs7757307	CCCATAATTCTTTAACTAAATAC	ACT
rs221635	ACAGTAAATGAAGGACATTGGC	ACG
rs4145418	TAGCCCTGTAAGCTGATC	CGT
rs221636		
rs3185958	CCACATCTTAAAGAGGCTGTT	ACT
rs4946654	GCCTATTGAAGAAATCATTTTAGA	CGT
rs221637	ACTTGAGCGATCCTCCAC	CGT
rs221638	CCTGGCTGAAAATCTTAAAAAAA	ACT
rs221639	GTGTGTGTGTGTGTGTAACCA	ACT
rs643545	CACCCGCATGTGTATGTATCT	ACT
rs221640	TCGTCTGAAGTCAGGAGTTC	ACT
rs3957696	TCTCTCTCTCTCTCTCAC	CGT
rs3995554	TCTCTCTCTCTCTCTCACAC	CGT
rs7453502	GAGTTTGTGTTTTAAAGAACTTTT	CGT
rs1190471	AAGAGTGATAAATGACCAGGC	ACT
rs221641	GAGATGTGAGCCACTGCGC	ACT
rs221642	CCAACCATGTGGAAGTGTGA	ACT
rs1190472	TTATCAACAGCATGAAAACGGA	ACG
rs1190473	CTGCACTCCAGCCCGGGA	ACT
rs186404	GGAGACACAGTGAGACTGTC	CGT
rs221643	AATGAAGAAGTCTTGCAATTTCTT	CGT
rs221644	CTAGCTCCAAGCCAGGTTAT	ACT
rs1203475	GCAGGAGAATCGCTTGAACC	ACG
rs221645	CAGACCTCAAAGTGGTCAAGA	ACT
rs170277	GACCCTTGCTAGCACTCAGA	ACG
rs221646	CAGGCAAACAGGTCCAGAG	ACG
rs221647	AGCTCCTTTCTTAGGTTATC	ACT
rs221648	GGCAACGGAGTGAGACCC	ACG
rs221649	AAGAAGAAGGCTGGGAGAAC	ACT
rs221650	GGCACAGTGGCTCACACTT	ACT
rs1149287	TCCCAGGCTGGTCTTGAAC	ACG
rs221651	AGCTGCAATGAGCTGTGATCG	ACG
rs7762591	CTTCCGTCTCCTGAGTTCCA	ACT
rs7748555	CAGGTGTGAGCCACCATGC	ACG
rs5878833	GCCTTCTGGCCATTTTTTTTTT	ACG
rs5878834	GCCTTCTGGCCATTTTTTTTTT	ACG
rs221652	TACTCAGGGAAGGATGTTACA	ACG
rs221653	TGTGTTAGCCAGGATGGTCT	ACG

dbSNP rs#	Extend Primer	Term Mix
rs221654	AAGACCATCCTGGCTAACAC	ACT
rs221655	GCTAACACGGTGAAACCCC	ACT
rs221656	CAGGCTGGAGTGTAGTGGC	ACT
rs221657	CACTTCCTCCCTCCGACTC	ACG
rs221658	TCAGCATTGTGGGCTGCC	ACT
rs110065	CTCCTTGCTGGTTGTGGCA	CGT
rs221659	ATGAATTCTATCTGTGCGACC	ACG
rs221660	GGAAACCAGGGCTTTTTTTTTT	ACT
rs7742821	ATTTCCATTTGTGTTGAGTCCT	ACT
rs221662	GAAATAAAAAGGAATCACACCC	ACT
rs7748426	CACATCTGTACTATTATTTCTACT	ACT
rs6911494	AGGCCAGGCTAACTGGGG	ACG
rs6939846	GTGGCCATGACAGTTGCAG	CGT
rs368471	TTATATTTCAAGGGAATGCTCTT	ACT
rs430190	GCCTCTGGGCAAAATTTCTGA	ACG
rs455114	TTTTTACAGTTGGGAGGCAGA	ACT
rs405956	AAGACTGGGACAGCAGCGA	ACT
rs5878835	GAACCACAGAAGGCCTTAAAAA	CGT
rs1473814	GAACCACAGAAGGCCTTAAAAA	CGT
rs423272	GTGGGTACATAGTGGATGTAT	ACT
rs413806	ACAGATTTACATCGTGGTACTC	ACG
rs4946655	GTAGCTTTGGCTTGTGCACC	ACT
rs6915632	CTTGACTCACTGCAACCTCA	ACT
rs2095723	TCTGTCCTCACACAGCATTTT	ACG
rs7450078	CGCTATGTTGCCAGGCTC	ACT
rs7453071	CCAAGGCAGGAGGATCTCT	ACT
rs1018810	CTGCTTTTATACATGCCACAC	ACT
rs7450944	GGGCTCCCTTTCCATCTCT	ACT
rs7748657	GTAGTGGCTGAATGCGATGT	ACT
rs1013137	CACTCCATACCAAATTAATATAC	ACG
rs5878836	GTGACACTGCTTGTAATTCTG	CGT
rs1981480	TACAATGGCAGTGACCCAGA	CGT
rs1981479	CTACAGGCCTGCACCACGA	ACG
rs3035187	ATGCCTGGCATTTTTTTTTTTTTT	CGT
rs7453993	GTGAGACCAACTCCCATCC	ACG
rs2001119	CTTACAAAAGCTTCTGTGCCAT	ACT
rs2001118	CAGCCAAAAACAACCCTAAAA	ACT
rs2001117	AAAAACAACCCTAAAAAGGAAGA	ACT
rs6940433	TGCCAAGAGGCACATTTTCC	ACT
rs1318746	AGGCTACTAAGTATATTTGATTTT	ACT
rs763099	AAAGACCTTCTGCCCATCCA	CGT
rs5878837	CGTATTCATCAGCAACAGCC	ACT
rs964731	ATACCCCTTTCTTCAGTAT	ACT
rs964730	TGAGGGATACTTGAGCTCTGT	ACT
rs6921869	GTCTCGAGCTCCTGGCCT	ACT
rs3945029	ATTAGCAGCCTCCTCCACTA	ACT
rs4945715	CTTCTCTTTCTCCTTTTTCATC	ACT
rs7775252	TTGAGAATTATTCCTGGTAATTA	ACT
rs7742098	CCAGAAAAGTGGCTTTGCCTT	ACT

dbSNP rs#	Extend Primer	Term Mix
rs3757289	AAAAATTCCACAGAGATGATGG	ACT
rs6905458	CCTCTCAGAAGTGTGCCAG	ACG
rs3757290	GACTGACTCTCTCCCCAAAA	ACT
rs2275289	AGGAACTCAGTGGCATGTAC	ACG
rs4945716	CTCACTGTGTTACCCAGGCT	ACT
rs6922638	GTGCTTTTGTTTCTTCTCATACT	ACT
rs7739572	AGACATTGGGTGTTTCTCTTTT	ACT
rs6901187	CTGACACATAGCTGCCAGAG	ACT
rs4946656	CTGTTGAAGAGCAAAGTTAACA	ACG
rs1338020	GCAAGACATTCTGAATAGTGC	ACT
rs7771472	GAAGGTGAATCTAGGGAATGAA	CGT
rs6926260	GTAAGCCACTGTGTCCAGC	ACG
rs6926627	AAGGCAGAGCAGGGTCCC	ACT
rs4946657	GTTTCATGTTGTATCTCTCTGT	ACT
rs6571218	CCTTATTAAAGAGAGAGAGAGA	ACT
rs7449944	GGCGGCAGCTGCTTGTTTC	ACT
rs952175	CTGGGCGCACTGCAACCT	ACT
rs1890228	CCATATCCTGGGCTATGTGT	ACG
rs1933237	CTTAGCCTCCAGAGTAGCTG	ACT
rs1338019	GTCACAAAGGGAGAACTCAAA	ACG
rs7453127	CTACTCTCTTAGCAAATTCAGTT	ACT
rs7381551	TTCCCACCCTTCAGCCCC	ACT
rs6571219	CGCTGGGGCAGAAAAAGAAA	ACG
rs6571220	TTCTTTTTCTGCCCCAGCGA	ACT
rs2185017	CAACACAGTGAGCAGTGAGA	ACG
rs1591720	GTGTGAGCCACCATGCCCA	ACT
rs6925046	GACAGGGTCTTGCTCTGTC	ACT
rs6940423	GGATTACAGATGTGAGCCAC	ACG
rs1190274	GGACAACACTTTTAAAGGTACT	ACT
rs1190276	CCAGCACTTTGGGAGGCC	ACT
rs1591719	TTGAATCTCTTTTAGAGTATGG	ACT
rs1933236	ATTTCTGATTCACACTGTAATA	ACG
rs6905202	GAAATTTTTCACGTTTGAAGGT	ACG
rs1209150	TGACCTGGAGGGAGAAAAAG	CGT
rs1190277	GCTAAGCACCACGGAGATAC	ACT
rs6926278	CTCCCACCTCAGCCTCCC	ACG
rs1190278	GGGTAGTCGGTAAAGGGGA	ACG
rs4626463	AGGGACTTTCCACACTAACC	ACT
rs6924620	TAAATATTCATTGCATAGAAGGAA	ACT
rs1190280	ATGCTGCATGTATTTATGGC	ACT
rs4557552	ACCCAGTACTTCCTCTCC	ACG
rs6932711	GTCATCACTCCCGCAGTTCA	ACG
rs1686140	CCCTTCCTTTGAAAACCTGG	ACT
rs1190281	TTTAAATGTGCAGTTACTTGATG	ACG
rs2308162	CCTCCAGTGAAAGCAATTATTT	CGT
rs1190282	GCTGAGAATACTTGCTGGCT	ACT
rs1765907	TGAGAAGCAACTCCTGAGTC	ACG
rs5878838	TGCCAATTAGCACTGAAAAAAG	ACT
rs1190283	CTACAAAATTCGTTACTACATAC	ACT

dbSNP rs#	Extend Primer	Term Mix
rs1190284	CAGACGTGGCAGCAGAGTAA	ACT
rs1190285	GTCACAGACATAGCCATTAGA	ACT

Genetic Analysis

[0292] Allelotyping results from the discovery cohort are shown for cases and controls in Table 41. The allele frequency for the A2 allele is noted in the fifth and sixth columns for osteoarthritis case pools and control pools, respectively, where “AF” is allele frequency. The allele frequency for the A1 allele can be easily calculated by subtracting the A2 allele frequency from 1 (A1 AF = 1-A2 AF). For example, the SNP rs1474555 has the following case and control allele frequencies: case A1 (C) = 0.64; case A2 (T) = 0.36; control A1 (C) = 0.70; and control A2 (T) = 0.30, where the nucleotide is provided in paranthesis. Some SNPs are labeled “untyped” because of failed assays.

TABLE 41

dbSNP rs#	Position in SEQ ID NO: 7	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs2400080	241	105557091	A/G			
rs6930209	801	105557651	A/G			
rs221628	899	105557749	A/G	0.716	0.755	0.216
rs221629	2091	105558941	C/G	0.775	0.801	0.338
rs221630	2290	105559140	C/T	0.066	0.049	0.465
rs221631	2440	105559290	A/G	0.147	0.137	0.686
rs1149284	4959	105561809	G/T			
rs221633	7914	105564764	C/G	0.094	0.091	0.911
rs423366	7969	105564819	A/G	0.392	0.418	0.448
rs436460	7972	105564822	C/T	0.186	0.175	0.720
rs2211010	10831	105567681	C/T			
rs379908	12399	105569249	C/T	0.773	0.809	0.242
rs1149285	13841	105570691	C/T			
rs7341194	14461	105571311	C/T			
rs715153	14680	105571530	C/T			
rs221634	16808	105573658	A/T	0.330	0.314	0.630
rs7757307	18231	105575081	C/T			
rs221635	18394	105575244	C/T			
rs4145418	18505	105575355	G/T	0.380	0.377	0.929
rs221636	18684	105575534	A/T	0.807	0.829	0.458
rs3185958	19257	105576107	C/T			
rs4946654	20263	105577113	A/T			
rs221637	20656	105577506	A/C	0.879	0.901	0.409
rs221638	21499	105578349	A/G	0.089	0.072	0.427
rs221639	21563	105578413	A/C	0.934	0.951	0.537
rs643545	21612	105578462	C/G	0.824	0.842	0.486
rs221640	21834	105578684	C/T			
rs3957696	22406	105579256	A/T			
rs3995554	22408	105579258	A/T			
rs7453502	22685	105579535	A/T			
rs1190471	23303	105580153	C/T			
rs221641	23306	105580156	C/G	0.070	0.053	0.415
rs221642	25139	105581989	A/G	0.868	0.869	0.987
rs1190472	25211	105582061	C/T	0.227	0.191	0.244
rs1190473	25364	105582214	A/G	0.722	0.742	0.521
rs186404	25381	105582231	A/C			
rs221643	25414	105582264	A/T	0.550	0.766	~0.0001
rs221644	25835	105582685	C/T	0.695	0.774	0.007
rs1203475	26214	105583064	A/G			

dbSNP rs#	Position in SEQ ID NO: 7	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs221645	27224	105584074	A/G	0.066	0.048	0.344
rs170277	27526	105584376	A/G	0.840	0.882	0.137
rs221646	27934	105584784	C/T	0.866	0.897	0.244
rs221647	28550	105585400	C/T	0.844	0.884	0.102
rs221648	29015	105585865	A/G	0.865	0.891	0.341
rs221649	29879	105586729	G/T	0.102	0.081	0.359
rs221650	29979	105586829	A/G	0.856	0.887	0.192
rs1149287	30030	105586880	A/G			
rs221651	30585	105587435	C/T	0.177	untyped	NA
rs7762591	31753	105588603	C/G			
rs7748555	31934	105588784	C/T	0.670	0.712	0.199
rs5878833	33227	105590077	-/T	0.140	0.113	0.338
rs5878834	33228	105590078	-/T	0.142	0.114	0.309
rs221652	35172	105592022	C/T	0.172	0.120	0.064
rs221653	36901	105593751	A/G			
rs221654	36921	105593771	A/G			
rs221655	36932	105593782	A/G			
rs221656	37061	105593911	C/T			
rs221657	37570	105594420	C/T	0.924	0.953	0.218
rs221658	38745	105595595	G/T	0.043	0.028	0.421
rs110065	38970	105595820	A/T	0.834	0.894	0.031
rs221659	39725	105596575	C/T	0.048	0.027	0.347
rs221660	40070	105596920	A/C	0.841	0.878	0.133
rs7742821	40460	105597310	C/G			
rs221662	41470	105598320	A/G	0.778	0.879	~0.0001
rs7748426	41562	105598412	A/G			
rs6911494	41956	105598806	A/G	0.043	0.032	0.652
rs6939846	42047	105598897	A/T			
rs368471	42280	105599130	A/G	0.150	0.104	0.074
rs430190	42358	105599208	A/G	0.053	0.033	0.386
rs455114	42629	105599479	C/G	0.059	0.027	0.100
rs405956	43075	105599925	C/T	0.132	0.089	0.063
rs5878835	43387	105600237	-/A			
rs1473814	43393	105600243	G/T	0.126	untyped	NA
rs423272	43438	105600288	C/T	0.023	untyped	NA
rs413806	44115	105600965	A/G	0.837	0.895	0.037
rs4946655	44537	105601387	A/G	0.062	0.033	0.128
rs6915632	45642	105602492	A/G			
rs2095723	46629	105603479	A/G			
rs7450078	47496	105604346	A/G	0.261	0.163	0.001
rs7453071	47515	105604365	A/C			
rs1018810	48329	105605179	A/G			
rs7450944	48862	105605712	C/G			
rs7748657	48908	105605758	A/G	0.972	untyped	NA
rs1013137	49038	105605888	C/T	0.699	0.785	0.006
rs5878836	49080	105605930	-/T			
rs1981480	50204	105607054	A/T	0.880	0.946	0.012
rs1981479	50404	105607254	A/G	0.052	0.035	0.453
rs3035187	50426	105607276	-/TTA	0.033	untyped	NA
rs7453993	50531	105607381	C/T	0.170	0.135	0.222
rs2001119	50840	105607690	C/T	0.176	0.122	0.033
rs2001118	50964	105607814	C/T	0.793	0.883	0.001
rs2001117	50971	105607821	C/T	0.575	0.650	0.035
rs6940433	51378	105608228	C/T			
rs1318746	52610	105609460	A/C	0.140	0.089	0.171
rs763099	53906	105610756	A/T	0.865	0.922	0.029
rs5878837	53951	105610801	-/C	0.423	0.463	0.215
rs964731	54111	105610961	A/C	0.865	0.926	0.089
rs964730	54149	105610999	G/T	0.903	0.951	0.022
rs6921869	55563	105612413	C/G			
rs3945029	55999	105612849	C/T	0.972	0.976	0.820
rs4945715	58415	105615265	C/G	0.057	0.021	0.048
rs7775252	58961	105615811	C/G	0.027	untyped	NA
rs7742098	60447	105617297	C/T			

dbSNP rs#	Position in SEQ ID NO: 7	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3757289	61377	105618227	A/G			
rs6905458	61528	105618378	A/G	0.045	0.023	0.345
rs3757290	61606	105618456	C/G			
rs2275289	62140	105618990	A/G			
rs4945716	62461	105619311	C/T			
rs6922638	63826	105620676	C/T	0.086	0.054	0.120
rs7739572	64950	105621800	G/T	0.920	0.931	0.613
rs6901187	65076	105621926	G/T	0.054	0.026	0.122
rs4946656	66121	105622971	C/T			
rs1338020	66406	105623256	C/T	0.109	0.077	0.145
rs7771472	67051	105623901	A/C	0.035	untyped	NA
rs6926260	68860	105625710	C/T	0.921	0.952	0.196
rs6926627	69014	105625864	C/T			
rs4946657	70796	105627646	C/T	0.224	0.136	0.001
rs6571218	72325	105629175	G/T	0.589	0.677	0.011
rs7449944	73414	105630264	A/C			
rs952175	75258	105632108	C/G	0.650	0.730	0.007
rs1890228	76347	105633197	A/G	0.046	0.028	0.426
rs1933237	76839	105633689	A/C	0.925	0.953	0.175
rs1338019	77358	105634208	A/G	0.888	0.930	0.101
rs7453127	77822	105634672	A/G	0.415	0.534	0.002
rs7381551	77946	105634796	G/T	0.026	untyped	NA
rs6571219	80002	105636852	A/G	0.837	0.903	0.017
rs6571220	80024	105636874	A/G	0.464	untyped	NA
rs2185017	80285	105637135	A/G	0.066	0.036	0.196
rs1591720	80397	105637247	C/G	0.027	untyped	NA
rs6925046	82075	105638925	C/T			
rs6940423	82153	105639003	A/G	0.024	0.029	0.840
rs1190274	83981	105640831	A/G	0.067	0.041	0.183
rs1190276	84184	105641034	A/G			
rs1591719	85089	105641939	C/T			
rs1933236	85288	105642138	A/G	0.892	0.942	0.046
rs6905202	85330	105642180	C/T	0.888	0.909	0.435
rs1209150	85581	105642431	A/T	0.862	0.922	0.023
rs1190277	85642	105642492	A/G	0.158	0.118	0.098
rs6926278	86433	105643283	A/G			
rs1190278	86904	105643754	A/G	0.211	0.147	0.030
rs4626463	88391	105645241	A/G	0.067	0.050	0.383
rs6924620	89042	105645892	C/T			
rs1190280	90828	105647678	G/T	0.890	0.948	0.008
rs4557552	92676	105649526	C/T	0.033	0.025	0.736
rs6932711	92881	105649731	C/T			
rs1686140	94227	105651077	G/T			
rs1190281	94585	105651435	A/G	0.914	0.950	0.140
rs2308162	94616	105651466	-ATAA	0.127	0.072	0.035
rs1190282	94712	105651562	C/G	0.879	0.937	0.009
rs1765907	94738	105651588	A/G	0.095	0.058	0.143
rs5878838	95253	105652103	-IG			
rs1190283	95522	105652372	A/G	0.054	0.032	0.245
rs1190284	95869	105652719	G/T	0.858	0.921	0.005
rs1190285	97856	105654706	C/T	0.908	0.957	0.017
rs6931398			A/G			

[0293] Allelotyping results were considered particularly significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The allelotyping p-values were plotted in Figure 1F for the discovery cohort. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele

frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figure 1F can be determined by consulting Table 41. For example, the left-most X on the left graph is at position 105557091. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0294] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The generally bottom-most curve is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0295] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is placed at the 3' end of each gene to show the direction of transcription.

Example 10

TM7SF3 Region Proximal SNPs

[0296] It has been discovered that SNP rs1484086 in *TM7SF3* is associated with occurrence of osteoarthritis in subjects. *TM7SF3* is an orphan receptor and is a member of the superfamily of 7-transmembrane domain proteins, one of the largest superfamilies of cell surface proteins. Members of this family include receptors for a variety of ligands, such as peptides, hormones, and ions, and for external sensory stimuli, such as odorants and light. Many 7-transmembrane molecules are able to recruit small G proteins, suggesting that they can transduce external signals to the cytoplasm.

[0297] Thirty-seven additional allelic variants proximal to rs1484086 were identified and subsequently allelotyped in osteoarthritis case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 42. The chromosome positions provided in column four of Table 42 are based on Genome "Build 34" of NCBI's GenBank.

TABLE 42

dbSNP rs#	Chromosome	Position in SEQ ID NO: 8	Chromosome Position	Allele Variants
rs1058701	12	230	27004780	a/c
rs11613	12	231	27004781	c/g
rs900743	12	5330	27009880	g/t
rs2129091	12	6334	27010884	a/c
rs15556	12	11372	27015922	c/t
rs1053724	12	11456	27016006	g/t
rs9699	12	11501	27016051	a/g
rs4856	12	13393	27017943	c/t
rs3782314	12	16666	27021216	a/g
rs2087736	12	17596	27022146	c/t
rs2068372	12	19710	27024260	a/g
rs2068371	12	19800	27024350	a/g
rs1184529	12	20297	27024847	a/g
rs2101256	12	20967	27025517	g/t
rs1552257	12	32514	27037064	c/t
rs1565585	12	33159	27037709	a/g
rs4080800	12	37600	27042150	a/g
rs1388658	12	41259	27045809	a/g
rs3782316	12	41329	27045879	c/t
rs1484086	12	50060	27054610	c/t
rs1484087	12	53292	27057842	c/t
rs2291549	12	53393	27057943	a/g
rs1565584	12	56417	27060967	c/t
rs3071166	12	56435	27060985	-/tt
rs1907652	12	58847	27063397	a/t
rs3759119	12	59595	27064145	c/t
rs3759120	12	59661	27064211	g/t
rs3782317	12	60355	27064905	c/t
rs3825166	12	60407	27064957	a/c
rs1872191	12	62357	27066907	a/g
rs8628	12	68230	27072780	g/t
rs1872193	12	68516	27073066	a/g
rs1042833	12	69055	27073605	c/t
rs2476	12	72603	27077153	c/g
rs1976206	12	73928	27078478	a/g
rs1388659	12	85897	27090447	c/t
rs1184528	12	91554	27096104	a/g

Assay for Verifying and Allelotyping SNPs

[0298] The methods used to verify and allelotype the 37 proximal SNPs of Table 42 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 43 and Table 44, respectively.

TABLE 43

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs1058701	ACGTTGGATGCTTCTCTCCAGTCCATGTTG	ACGTTGGATGGTAACAAGTCCGAAGGATTG
rs11613	ACGTTGGATGTCCAAGTGCCTTCTCTCCAG	ACGTTGGATGTCTTGTATGCATCTCGACAC
rs900743	ACGTTGGATGAACAGATCCGGAACTTTTT	ACGTTGGATGGGCTCATAGAACCCTTTTT
rs2129091	ACGTTGGATGTTAAATTGGTATGGTCTCC	ACGTTGGATGGTTTTGCACTAAGAAGAGAC
rs15556	ACGTTGGATGTGTAGGGACAAAGTTATATGGAA	ACGTTGGATGTGTCTTTACAGTCTTCACTGGCA
rs1053724	ACGTTGGATGCCATATAACTTTGTCCCTAC	ACGTTGGATGAAAATACAGTGCAGGTGACC
rs9699	ACGTTGGATGTTTCAGTGTTACTGAAGTTAATT	ACGTTGGATGCAACATAGAAAATATAAAACAATTT
rs4856	ACGTTGGATGTTGTAAACCAAAAGGTAATTTCTCA	ACGTTGGATGGATGACCAAAAGGTTGGTGG
rs3782314	ACGTTGGATGAATGCTGCACAACCTAGGCC	ACGTTGGATGAGCAGTCAGCCTATTCTTGC
rs2087736	ACGTTGGATGCAGTGAGACTCTGTCTCTAC	ACGTTGGATGTACATCAGCCTCCCAAGTAG
rs2068372	ACGTTGGATGCTAGAGAGGGTTGCTCTATG	ACGTTGGATGCCAGCTTCAGCTTCTGTAG
rs2068371	ACGTTGGATGATTGACAAGCCAAGCCTGTC	ACGTTGGATGATAGAGCAACCCCTCTCTAGG
rs1184529	ACGTTGGATGTTCTTTTCTGGTGGTTTGC	ACGTTGGATGGGTGTCAGTCTTGTATCAG
rs2101256	ACGTTGGATGCTGGGTTTTTTTGGTGTGTTG	ACGTTGGATGCTTGTACTGTATCTCAATTTT
rs1552257	ACGTTGGATGCAATACCTTAGCTCACCTAC	ACGTTGGATGCATTAGGGAAAATCTGGATC
rs1565585	ACGTTGGATGGCTAGAATATACCACAGGTG	ACGTTGGATGTCACTGAAAATGGATCAGCC
rs4080800	ACGTTGGATGGGGTTCAAGCAATTCTCCTG	ACGTTGGATGAAAATTAGCCAGGTGTGGTG
rs1388658	ACGTTGGATGAAAAGAGAGAGGATGGGTG	ACGTTGGATGCAGGAGCTTAAGAACCACTG
rs3782316	ACGTTGGATGGTCTTGCTGTAATGTCATTAG	ACGTTGGATGCTTCTCTTTTAACTAGATC
rs1484086	ACGTTGGATGTGCTACTCTTCGGAAGTCTC	ACGTTGGATGCATGTACAGGGCATTACAG
rs1484087	ACGTTGGATGGCATGGAATTTTACACCCC	ACGTTGGATGTTCCCTCTCAAACCTCTGTAG
rs2291549	ACGTTGGATGACTAAAGCGCCTCTTTGCTG	ACGTTGGATGCATTAAGCCGCTAGTTCCAC
rs1565584	ACGTTGGATGAAAAGGCAAGTTATGATGC	ACGTTGGATGAGTATCCATTCTCTGAGTC
rs3071166	ACGTTGGATGAAAAGGCAAGTTATGATGC	ACGTTGGATGAGTATCCATTCTCTGAGTC
rs1907652	ACGTTGGATGCCATATTTCCAGTACCTAGC	ACGTTGGATGGGTTGATAAATATGTGCCAG
rs3759119	ACGTTGGATGCTAAACTGTTCTTAGTGCCG	ACGTTGGATGGGGAATTTCAAAGAGTGTGG
rs3759120	ACGTTGGATGCGGCACTAAGAACAGTTTAGA	ACGTTGGATGGGTTTTTATGACTGTAGCAAC
rs3782317	ACGTTGGATGGGAAGCTCTTGAAGCTGTAG	ACGTTGGATGGCCATTGAGAAATCCTGAGC
rs3825166	ACGTTGGATGACCAGACTCTCAACTTAGCC	ACGTTGGATGTGGCAGGTGGGTTATTCTTG
rs1872191	ACGTTGGATGTTTATGCCGAAGCCCTGTCT	ACGTTGGATGTAAAGCAAGGGAGGAAAGGG
rs8628	ACGTTGGATGCAAGCCTTACCAACAATTACAGAA	ACGTTGGATGGCTTATCAAGAGTGAAAATAGAAGA
rs1872193	ACGTTGGATGAATGCCACCTCTAAGAGGCA	ACGTTGGATGCTCAAGCCAAAGGAGAAGAC
rs1042833	ACGTTGGATGTCATCCAACCCCTGGATCTC	ACGTTGGATGATACAGCCCCAGGAAATAGC
rs2476	ACGTTGGATGAGGAGCAGGTGACGTTAATG	ACGTTGGATGATTGACTAGCCACCAGGAAG
rs1976206	ACGTTGGATGAGCTGGGATTGGATTACAGG	ACGTTGGATGATGGAGAAACCCCGTCTCTA
rs1388659	ACGTTGGATGACCTCAGCCTTCCACATTTG	ACGTTGGATGAGCAGGAGGAACTTTTGGG
rs1184528	ACGTTGGATGTGAGAATCGCTTGAACCCAG	ACGTTGGATGTTTGAATCAGAGTCTCCCTC

TABLE 44

dbSNP rs#	Extend Primer	Term Mix
rs1058701	CCAGTCCATGTTGAGGTGC	ACT
rs11613	CCAGTCCATGTTGAGGTG	ACT
rs900743	ATCCGGAACTTTTTTTTTGAATTT	ACT
rs2129091	ATTTAATTTGAAAAGTGCTTACCC	ACT
rs15556	GTTTGTATTCTTCTATAC	ACG
rs1053724	CATCAAGTTTCAAGTGTAA	CGT
rs9699	TACAGAATAAGCAGTAAA	ACG
rs4856	CAAGTATTTGGAAATAAG	ACT

dbSNP rs#	Extend Primer	Term Mix
rs3782314	ACAAATATATGAGAACTCCTCTTT	ACT
rs2087736	ACTCTGTCTCTACTAAAAATAAAA	ACT
rs2068372	TGGCTTCATGGCACCCTG	ACT
rs2068371	AGCCAAGCCTGTCACTGGCCCT	ACT
rs1184529	TCCTGGTGGTTTGCCACTTA	ACT
rs2101256	GTTTTTTTGGTGTGTTGATATGTA	ACT
rs1552257	AGCTCACCTACGAAAATGAATAA	ACG
rs1565585	TGTCAGACTGCACTACAT	ACT
rs4080800	ATTCTCCTGTCTCAGCCTCC	ACG
rs1388658	GAGAGGATGGGTGAAATAAGG	ACT
rs3782316	TGTAATGTCATTAGGAAGAAACA	ACG
rs1484086	CTCTTCGGAAGTCTCTTTCTCA	ACT
rs1484087	TTTACACCCCCAAATCTAGAG	ACT
rs2291549	CCTCTTTGCTGCCCAGTGG	ACT
rs1565584	TGATGCAATAAGTATATATAGTAC	ACT
rs3071166	TAGTACGTGGCTTTTTTTTTTTTTT	CGT
rs1907652	TCCAGTACCTAGCACCTAAC	CGT
rs3759119	TTAGTGCCGGGATGAATAACT	ACT
rs3759120	AAATTGCAACTGTGAGTATTAAAG	ACT
rs3782317	AGAATAACCCACCTGCCAAAT	ACT
rs3825166	ACTTAGCCTACATTTGAAAAGGG	ACT
rs1872191	CTCAGTCCGCTCCCCACTT	ACG
rs8628	TTAAACACTATGACACAT	ACG
rs1872193	AGAGGCAGGACACTAGCC	ACG
rs1042833	CCCTTGGATCTCTTTGAG	ACG
rs2476	GTGACGTTAATGGGACAGCT	ACT
rs1976206	TACAGGCGCCCAACCACCA	ACG
rs1388659	CCACATTTGGTAAGTTTGGACAT	ACT
rs1184528	AGAGGTTGCAGAGAGCCAAGATC	ACT

Genetic Analysis

[0299] Allelotyping results from the discovery cohort are shown for cases and controls in Table 45. The allele frequency for the A2 allele is noted in the fifth and sixth columns for osteoarthritis case pools and control pools, respectively, where “AF” is allele frequency. The allele frequency for the A1 allele can be easily calculated by subtracting the A2 allele frequency from 1 (A1 AF = 1-A2 AF). For example, the SNP rs900743 has the following case and control allele frequencies: case A1 (G) = 0.92; case A2 (T) = 0.08; control A1 (G) = 0.90; and control A2 (T) = 0.10, where the nucleotide is provided in paranthesis. Some SNPs are labeled “untyped” because of failed assays.

TABLE 45

dbSNP rs#	Position in SEQ ID NO: 8	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1058701	230	27004780	A/C			
rs11613	231	27004781	C/G			
rs900743	5330	27009880	G/T	0.08	0.10	0.381

dbSNP rs#	Position in SEQ ID NO: 8	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs2129091	6334	27010884	A/C	0.19	0.20	0.646
rs15556	11372	27015922	C/T	0.74	0.74	0.923
rs1053724	11456	27016006	G/T	0.14	0.15	0.592
rs9699	11501	27016051	A/G	0.67	0.68	0.595
rs4856	13393	27017943	C/T	0.10	0.09	0.474
rs3782314	16666	27021216	A/G	0.20	0.22	0.278
rs2087736	17596	27022146	C/T			
rs2068372	19710	27024260	A/G	0.11	0.10	0.634
rs2068371	19800	27024350	A/G			
rs1184529	20297	27024847	A/G			
rs2101256	20967	27025517	G/T			
rs1552257	32514	27037064	C/T	0.67	0.67	0.969
rs1565585	33159	27037709	A/G	0.69	0.65	0.064
rs4080800	37600	27042150	A/G			
rs1388658	41259	27045809	A/G	0.35	0.38	0.362
rs3782316	41329	27045879	C/T	0.47	0.46	0.740
rs1484086	50060	27054610	C/T			
rs1484087	53292	27057842	C/T	0.35	0.38	0.127
rs2291549	53393	27057943	A/G			
rs1565584	56417	27060967	C/T	0.66	0.69	0.327
rs3071166	56435	27060985	-/TT	0.52	0.47	0.042
rs1907652	58847	27063397	A/T	0.64	0.64	0.984
rs3759119	59595	27064145	C/T	0.08	0.05	0.042
rs3759120	59661	27064211	G/T	0.15	0.14	0.861
rs3782317	60355	27064905	C/T	0.08	0.07	0.780
rs3825166	60407	27064957	A/C	0.83	0.84	0.660
rs1872191	62357	27066907	A/G	0.04	0.05	0.555
rs8628	68230	27072780	G/T	0.59	0.61	0.411
rs1872193	68516	27073066	A/G	0.92	0.91	0.669
rs1042833	69055	27073605	C/T	0.85	0.86	0.605
rs2476	72603	27077153	C/G	0.81	0.82	0.392
rs1976206	73928	27078478	A/G	0.16	0.15	0.781
rs1388659	85897	27090447	C/T	0.49	0.50	0.692
rs1184528	91554	27096104	A/G	0.20	0.17	0.228

[0300] The *TM7SF3* proximal SNPs were also allelotyped in the replication cohorts using the methods described herein and the primers provided in Tables 43 and 44. The replication allelotyping results for replication cohort #1 and replication cohort #2 are provided in Tables 46 and 47, respectively.

TABLE 46

dbSNP rs#	Position in SEQ ID NO: 8	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1058701	230	27004780	A/C			
rs11613	231	27004781	C/G			
rs900743	5330	27009880	G/T	0.07	0.11	0.258
rs2129091	6334	27010884	A/C	0.18	0.20	0.450
rs15556	11372	27015922	C/T	0.73	0.74	0.858
rs1053724	11456	27016006	G/T	0.15	0.15	0.969
rs9699	11501	27016051	A/G	0.65	0.68	0.290
rs4856	13393	27017943	C/T	0.11	0.10	0.735
rs3782314	16666	27021216	A/G	0.18	0.22	0.171
rs2087736	17596	27022146	C/T			
rs2068372	19710	27024260	A/G	0.11	0.11	0.867
rs2068371	19800	27024350	A/G			
rs1184529	20297	27024847	A/G			
rs2101256	20967	27025517	G/T			
rs1552257	32514	27037064	C/T	0.70	0.66	0.239
rs1565585	33159	27037709	A/G	0.67	0.65	0.599

dbSNP rs#	Position in SEQ ID NO: 8	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs4080800	37600	27042150	A/G			
rs1388658	41259	27045809	A/G	0.36	NA	NA
rs3782316	41329	27045879	C/T	0.45	0.49	0.230
rs1484086	50060	27054610	C/T			
rs1484087	53292	27057842	C/T	0.32	0.40	0.023
rs2291549	53393	27057943	A/G			
rs1565584	56417	27060967	C/T	0.61	0.65	0.297
rs3071166	56435	27060985	-/TT	0.55	0.45	0.003
rs1907652	58847	27063397	A/T	0.62	NA	0.638
rs3759119	59595	27064145	C/T	0.09	0.04	0.025
rs3759120	59661	27064211	G/T	0.16	0.15	0.651
rs3782317	60355	27064905	C/T	0.07	0.07	0.986
rs3825166	60407	27064957	A/C	0.84	0.84	0.945
rs1872191	62357	27066907	A/G	0.04	0.06	0.562
rs8628	68230	27072780	G/T	0.58	0.64	0.060
rs1872193	68516	27073066	A/G	0.92	0.91	0.957
rs1042833	69055	27073605	C/T	0.85	0.86	0.746
rs2476	72603	27077153	C/G	0.81	0.84	0.397
rs1976206	73928	27078478	A/G	0.17	0.16	0.788
rs1388659	85897	27090447	C/T	0.47	0.50	0.283
rs1184528	91554	27096104	A/G	0.21	0.16	0.170

TABLE 47

dbSNP rs#	Position in SEQ ID NO: 8	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1058701	230	27004780	A/C			
rs11613	231	27004781	C/G			
rs900743	5330	27009880	G/T	0.10	0.09	0.763
rs2129091	6334	27010884	A/C	0.21	0.20	0.896
rs15556	11372	27015922	C/T	0.75	0.75	0.974
rs1053724	11456	27016006	G/T	0.12	0.15	0.373
rs9699	11501	27016051	A/G	0.69	0.67	0.615
rs4856	13393	27017943	C/T	0.10	0.08	0.413
rs3782314	16666	27021216	A/G	0.22	0.22	0.944
rs2087736	17596	27022146	C/T			
rs2068372	19710	27024260	A/G	0.11	0.10	0.561
rs2068371	19800	27024350	A/G			
rs1184529	20297	27024847	A/G			
rs2101256	20967	27025517	G/T			
rs1552257	32514	27037064	C/T	0.63	0.68	0.247
rs1565585	33159	27037709	A/G	0.73	0.66	0.029
rs4080800	37600	27042150	A/G			
rs1388658	41259	27045809	A/G	0.33	0.38	0.217
rs3782316	41329	27045879	C/T	0.51	0.42	0.036
rs1484086	50060	27054610	C/T			
rs1484087	53292	27057842	C/T	0.38	0.36	0.575
rs2291549	53393	27057943	A/G			
rs1565584	56417	27060967	C/T	0.73	0.74	0.635
rs3071166	56435	27060985	-/TT	0.48	0.49	0.727
rs1907652	58847	27063397	A/T	0.66	-0.02	
rs3759119	59595	27064145	C/T	0.06	0.05	0.669
rs3759120	59661	27064211	G/T	0.13	0.14	0.881
rs3782317	60355	27064905	C/T	0.08	0.07	0.655
rs3825166	60407	27064957	A/C	0.82	0.84	0.546
rs1872191	62357	27066907	A/G	0.04	0.04	0.894
rs8628	68230	27072780	G/T	0.61	0.56	0.234
rs1872193	68516	27073066	A/G	0.93	0.91	0.528
rs1042833	69055	27073605	C/T	0.85	0.86	0.682
rs2476	72603	27077153	C/G	0.80	0.81	0.829
rs1976206	73928	27078478	A/G	0.14	0.14	0.834
rs1388659	85897	27090447	C/T	0.51	0.48	0.499
rs1184528	91554	27096104	A/G	0.18	0.18	0.993

[0301] Allelotyping results were considered particularly significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The allelotyping p-values were plotted in Figure 1G for the discovery cohort. The position of each SNP on the chromosome is presented on the x-axis. The y-axis provides the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figure 1G can be determined by consulting Table 45. For example, the left-most X on the left graph is at position 27004780. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0302] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The generally bottom-most curve is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0303] The exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is placed at the 3' end of each gene to show the direction of transcription.

Example 11

LOXLI Region Proximal SNPs

[0304] It has been discovered that rs8818 in the untranslated region (UTR) of the lysyl oxidase-like 1 (*LOXLI*) gene is associated with occurrence of osteoarthritis in subjects. *LOXLI* is a Lysyl oxidase-like protein that catalyzes the cross-linking of collagen via lysine residues. Deficiency of the related protein, lysyl oxidase, causes a form of Ehlers-Danlos syndrome. *LOXLI* likely is a secreted protein and its biological activity may be modulated by addition of an antibody, a recombinant binding partner, a binding agent, or a recombinant *LOXLI* protein or functional fragment thereof.

[0305] Fifty-eight additional allelic variants proximal to rs912428 were identified and subsequently allelotyped in osteoarthritis case and control sample sets as described in Examples 1 and 2. The

polymorphic variants are set forth in Table 48. The chromosome positions provided in column four of Table 48 are based on Genome "Build 34" of NCBI's GenBank.

TABLE 48

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 10	Chromosome Position	Allele Variants
rs1048661	15	213	71935363	G/T
rs3825942	15	249	71935399	C/T
rs1550436	15	1824	71936974	C/T
rs1550438	15	2057	71937207	C/T
rs1550439	15	2306	71937456	A/T
rs2165241	15	2869	71938019	C/T
rs1550433	15	3976	71939126	A/C
rs3056314	15	4288	71939438	-/TC
rs2415204	15	4290	71939440	A/C
rs1992314	15	4434	71939584	C/G
rs1440101	15	5298	71940448	A/G
rs2289414	15	5467	71940617	A/G
rs2415205	15	8486	71943636	C/G
rs2899807	15	8487	71943637	A/T
rs893815	15	8831	71943981	C/G
rs3056342	15	9036	71944186	-/AG
rs4077284	15	9058	71944208	A/G
rs893816	15	9131	71944281	C/T
rs893817	15	9732	71944882	A/G
rs893818	15	9862	71945012	A/G
rs893819	15	10191	71945341	A/G
rs893820	15	10270	71945420	C/T
rs2304719	15	16167	71951317	C/T
rs1001507	15	17620	71952770	G/T
rs1530167	15	17751	71952901	C/T
rs1530168	15	17764	71952914	C/T
rs1530169	15	17787	71952937	C/T
rs2304720	15	19401	71954551	C/T
rs2304721	15	21021	71956171	A/C
rs893821	15	21902	71957052	C/T
rs750460	15	22173	71957323	C/T
rs2304722	15	22416	71957566	C/T
rs1440102	15	22653	71957803	A/G
rs8818	15	24945	71960095	C/G
rs3522	15	25011	71960161	C/T
rs2415206	15	28563	71963713	C/T
rs1984526	15	48574	71983724	C/G
rs1984525	15	48710	71983860	C/T
rs3031653	15	48880	71984030	-/TTG
rs2415187	15	50194	71985344	C/T
rs2507	15	56343	71991493	A/G
rs2289411	15	56455	71991605	C/T
rs3202077	15	56729	71991879	C/T
rs2289412	15	56759	71991909	A/G
rs2289413	15	56895	71992045	A/G
rs1061082	15	57036	71992186	C/G

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 10	Chromosome Position	Allele Variants
rs2277600	15	57702	71992852	C/G
rs734854	15	62515	71997665	C/T
rs2415188	15	62629	71997779	C/G
rs3214695	15	63501	71998651	-/C
rs3816197	15	63547	71998697	C/T
rs3816198	15	64876	72000026	C/G
rs2304715	15	65073	72000223	C/G
rs2301272	15	67149	72002299	C/T
rs2301273	15	67549	72002699	C/T
rs3784563	15	71660	72006810	A/C
rs3784561	15	71906	72007056	C/T
rs3784560	15	71911	72007061	A/C

Assay for Verifying and Allelotyping SNPs

[0306] The methods used to verify and allelotype the 58 proximal SNPs of Table 48 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 49 and Table 50, respectively.

TABLE 49

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs1048661	ACGTTGGATGTTGCTGGGAGACGGAGGTG	ACGTTGGATGATTCCGGCTTTGGCCAGGTGC
rs3825942	ACGTTGGATGTAGGTGCTGGCGAAGGCCGAA	ACGTTGGATGACCTCCGTCTCCAGCAAC
rs1130133	ACGTTGGATGACCAAGTCAGGGAGACCGCG	ACGTTGGATGAGCGGAACGGCGCGCAGCA
rs1550436	ACGTTGGATGCCAAAAAACTCAGTAACG	ACGTTGGATGGTTCAATTACAGATAGTTTTGC
rs1550437	ACGTTGGATGTTGGCCTTCCCAAGAGGAG	ACGTTGGATGAGAGCCCCAGCTGTGGACA
rs1550438	ACGTTGGATGAGTCAGCCCTTGTCACAGTA	ACGTTGGATGCATGAGGACACAGTGGAAAG
rs1550439	ACGTTGGATGATTCTCTGCTCCCCATTGAG	ACGTTGGATGTATACTCTGAGGCACTGGAG
rs2165241	ACGTTGGATGTAGAAGACCCACTGACTTGG	ACGTTGGATGGGGCAGAGAAAAGTCTGAGCTC
rs1550433	ACGTTGGATGATAGCAGGAGTGGTCACATC	ACGTTGGATGTAGCAAATCCTTGAAGAGAG
rs3056314	ACGTTGGATGTCTCTCCTGGCCTCTGATTG	ACGTTGGATGCCTGACGTGTGTCTCTATC
rs2415204	ACGTTGGATGTTCTCTCCTGGCCTCTGAT	ACGTTGGATGCCTGACGTGTGTCTCTATC
rs1992314	ACGTTGGATGTTTGTCTAAAGGCCCTGAG	ACGTTGGATGAGATAAACCCCTGCAGTCTG
rs1440101	ACGTTGGATGAAAAGTCAGCAAGTGAGCTC	ACGTTGGATGTTAATTCAGGTCTAGCC
rs2289414	ACGTTGGATGTTGCTTATCTGTACACCTC	ACGTTGGATGCTCACCTGTACAAACAGT
rs2415205	ACGTTGGATGTGATGCTTCAGTTACTCCAG	ACGTTGGATGTGTGGCAGCGTAAGTTTTG
rs2899807	ACGTTGGATGTGATGCTTCAGTTACTCCAG	ACGTTGGATGTGTGGCAGCGTAAGTTTTG
rs893815	ACGTTGGATGCACCTTTTACAGCACTCAC	ACGTTGGATGATCCCTTCTGTGAGTCAAGC
rs3056342	ACGTTGGATGTAAGGATCAGTAGGCAGGTC	ACGTTGGATGATAGCTGGGAATTCAGGAC
rs4077284	ACGTTGGATGTAAGGATCAGTAGGCAGGTC	ACGTTGGATGATAGCTGGGAATTCAGGAC
rs893816	ACGTTGGATGATTGCCACAGAATCAAGCC	ACGTTGGATGTTCTGGAAGGCTAGGTAAGG
rs893817	ACGTTGGATGAAACAGGTGAGGTGTGGACG	ACGTTGGATGAGAAATCTGTTCCCTCCTGC
rs893818	ACGTTGGATGTTTTAGGAGCTGTTCAATTG	ACGTTGGATGTGGGAGAATTCCTGACTGC
rs893819	ACGTTGGATGCTGTACACTGACTCTTGGG	ACGTTGGATGATGGTCTTTGTCTCCGGTT
rs893820	ACGTTGGATGAGAGTCAGTGTGACAGGTTG	ACGTTGGATGTTCTATATCCTGGCTCTGCC
rs2304719	ACGTTGGATGTTTCATCAGTGAGCCTTGCC	ACGTTGGATGCCCTGTATAGTGAGGTACAG
rs1001507	ACGTTGGATGAGAATCCTGCAAAACTGGAG	ACGTTGGATGTGCAGCATGTGAACTGGCAC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs1530167	ACGTTGGATGAAACATCCTCCTTCCCTCTG	ACGTTGGATGGCCTAGAACCTAGACCCCTTA
rs1530168	ACGTTGGATGCAAAACATCCTCCTTCCCTC	ACGTTGGATGGACCCTTATGGTTTCCCATG
rs1530169	ACGTTGGATGTGTGCTGAGCTGAACAGAAG	ACGTTGGATGGGAATCTGTCTATGTCTGGG
rs2304720	ACGTTGGATGATGCTGGGTTCTGGTGTAC	ACGTTGGATGATAGGCTGTGCTGCAGGGAC
rs2304721	ACGTTGGATGCTCAAGTGATGCCTCAGATG	ACGTTGGATGCTGAAAGAAGCTTCAGCCTC
rs893821	ACGTTGGATGTGGATTAAGTGGGTAGGGC	ACGTTGGATGGAAAGTGCATCCCTGCATC
rs750460	ACGTTGGATGATGTTTCCCTAGAGCTAGAG	ACGTTGGATGCTCAGCTCCTCATTACTGCA
rs2304722	ACGTTGGATGTTACCACCTTCTCTGGTGAG	ACGTTGGATGGAGGAAGAAGAGAAACAGGG
rs1440102	ACGTTGGATGAGTAAGAGTTTGCCACCAC	ACGTTGGATGTGACCTAAAGTGCAGGTATC
rs8818	ACGTTGGATGAATCTCTCCCTTCCAAAGC	ACGTTGGATGTCCCTGTGGTTTTCATCCAC
rs3522	ACGTTGGATGAACAACACTGTAGAGAAAAGTGAA	ACGTTGGATGACGTGGATGAAAACACAGG
rs2415206	ACGTTGGATGCACCTTGAGGTGAAACAGAC	ACGTTGGATGTTACTTAGTAGACCCCGAGG
rs1984526	ACGTTGGATGATCCTTTGTTCTTGAAACAG	ACGTTGGATGGGATTACAAACGTGAGCCAC
rs1984525	ACGTTGGATGCAGCTGGGATTACAGGTATG	ACGTTGGATGACCAACATGGTGAAACCTG
rs3031653	ACGTTGGATGATAAACGTTAAGCTCAGTTG	ACGTTGGATGAAAAAAAAGTGAAAGTCG
rs2415187	ACGTTGGATGTTCTATGAGTTACTTGACAC	ACGTTGGATGGTGTCTTTATCTGACTAGTG
rs2507	ACGTTGGATGGCTGCTCCCAAGATTCTG	ACGTTGGATGTAAGAAGCACAGAACGCAGG
rs2289411	ACGTTGGATGCTGTGGCGAAGTTACCTGGG	ACGTTGGATGTGCTCCTTCCCATGCCCAAT
rs3202077	ACGTTGGATGACAGTGGTCTCTGGACAAG	ACGTTGGATGTCTCCTCCTGGAATCACACC
rs2289412	ACGTTGGATGGGACAAAGCCTTGTCAGAG	ACGTTGGATGATGAATGGAGGCTGCAGGAG
rs2289413	ACGTTGGATGTTGGCTGACTTTCAGAGCC	ACGTTGGATGTGCAGATGAACACCTCCTCC
rs1061082	ACGTTGGATGGGCCCTGCTATGCAGAGAG	ACGTTGGATGAGGTCGCCCTTCACCTTCAG
rs2277600	ACGTTGGATGTAGTGAGGTCCAGGAAGTAG	ACGTTGGATGCCTGCTACCAGTTCAATGTC
rs734854	ACGTTGGATGATAACTCCAAAGGCCATGTG	ACGTTGGATGCAGACCACAGAGATGAAAAG
rs2415188	ACGTTGGATGAAAGTTGACAAAGCCCTTTC	ACGTTGGATGAGGAACTGTCTGTCTTGG
rs3214695	ACGTTGGATGACACTTGCCCAAGTTCACTC	ACGTTGGATGTACATCTGCAGGTGAGAGCA
rs3816197	ACGTTGGATGGTGAAGTTGGGCAAGTGAC	ACGTTGGATGAGATTGAGAGCCCTGAGAAG
rs3816198	ACGTTGGATGTAGGGTCATGGGGCTTTGG	ACGTTGGATGGGCTGATAAGAGCCGAGGAC
rs2304715	ACGTTGGATGGTGAGTGGCCGCCTGGCAC	ACGTTGGATGTCCTCGGAGGCAGAGATTGG
rs2301272	ACGTTGGATGATGATACCCAAAGGAGTGTC	ACGTTGGATGTCAGCAACTTCCCATCACTC
rs2301273	ACGTTGGATGACCTACCGCTGACTTACGG	ACGTTGGATGACGGATGAATGGATCAAAG
rs3784563	ACGTTGGATGAATGTGGTCTGCAGATATGC	ACGTTGGATGAACTTACTATCCACCTGCG
rs3784561	ACGTTGGATGATGACCACAATTTATGCTGC	ACGTTGGATGTGCAAAGATGATTCTGCAGC
rs3784561	ACGTTGGATGCAGTAAGGCTGGATTCTAGG	ACGTTGGATGGCTGCCTGGTGTAAATGGTT
rs3784560	ACGTTGGATGGCTGGATTCTAGGATCAGAG	ACGTTGGATGACATTCTCAGATAGCGCTGC

TABLE 50

dbSNP rs#	Extend Primer	Term Mix
rs1048661	GGAGACGGAGGTGCGGGCC	CGT
rs3825942	GAGACCGAGGAGGCGGAG	ACG
rs1130133	GGCCGGTACACGCTGCC	ACG
rs1550436	AAAAAACTCAGTAACGGAGATAA	ACT
rs1550437	TTCACCCCTGAAAAGCCAGA	ACT
rs1550438	GTAGCCCTGTCTGCTAACAGCAT	ACT
rs1550439	CTCCCCATTGAGGTTGCTG	CGT
rs2165241	CCAGGCATGCCTCTGCCA	ACT
rs1550433	GGTCACATCGAGGGAGCC	ACT
rs3056314	TGGCCTCTGATTGGCCATG	ACT

dbSNP rs#	Extend Primer	Term Mix
rs2415204	CTCCTGGCCTCTGATTGGCCA	ACT
rs1992314	AAGGCCCTGAGGAGCTACA	ACT
rs1440101	CTCGTCACCACATCTGTAACA	ACG
rs2289414	TTTATTCACTCATTCAATTTGGTC	ACT
rs2415205	CTCAGGCCCTGCACAGTGA	ACT
rs2899807	CTCAGGCCCTGCACAGTG	CGT
rs893815	ACAGCACTCACCTGTCCAC	ACT
rs3056342	CACACCCCAACCTTTTTTACCCC	ACT
rs4077284	GGCAGGTCTCTGGCAGCA	ACG
rs893816	CAGAGTGGCAGCTAAAGCC	ACT
rs893817	GGTGTGGACGAGCAATGGGAA	ACT
rs893818	AGCCCTCTCACAACCCCTACAGA	ACG
rs893819	CACCCTGTCTCTCTGCTCAA	ACG
rs893820	ACAGGTTCTCTCTACTGTGC	ACG
rs2304719	CAGGAGGGGAGGGGAGCAAG	ACG
rs1001507	GGCCCTCTGAGATCATTTCAA	ACT
rs1530167	CTGTTCAGCTCAGCACACC	ACT
rs1530168	CAGTTAAATCCTGCCCTTCTGTTC	ACT
rs1530169	TGAACAGAAGGGCAGGATTTAAC	ACG
rs2304720	TGTGCCCAACCCCCCCC	ACG
rs2304721	TCAGATGCTGCCTCTGCTC	ACT
rs893821	GCCAGCTTTATTTGCAGAATCT	ACT
rs750460	CAGAGAGGTTGGATCCTGCC	ACG
rs2304722	CTCTGGTGAGCAGTTGAGG	ACG
rs1440102	GCAAGCAAGGCCACCTGA	ACT
rs8818	AGCCCCCAACCCACAGGCA	ACT
rs3522	TATAAAATGGGGTCTGGC	ACT
rs2415206	GAAACAGACCCCCACCCC	ACG
rs1984526	AGCATAAAGGTGAAAGATGGGCC	ACT
rs1984525	GGATTACAGGTATGCACCACCA	ACG
rs3031653	AAGCTCAGTTGTGGCTCCAAACAA	ACT
rs2415187	TCTTTTAAAAAACTACACCAGGT	ACG
rs2507	TGACTCATCTGCCAGCTC	ACG
rs2289411	GGGATCCTGGCTGGCCC	ACT
rs3202077	CTGGACAAGGCTTTGTCCAT	ACG
rs2289412	GCCTTGTCCAGAGAACCACT	ACT
rs2289413	CAAGCCTGGCACCAAGCC	ACG
rs1061082	CTATGCAGAGAGCTGCGGC	ACT
rs2277600	GGAAGTAGGCGCTTTGGGTG	ACT
rs734854	ACTCCAAAGGCCATGTGTCTTAAC	ACG
rs2415188	GGGGTGCTGTTAGGGCAGCC	ACT
rs3214695	CGCTTGGCAGCTGTCGTG	ACT
rs3816197	CTTGCGCAAGTGTACCTTACG	ACG
rs3816198	CCCCAGAGCCAGCCAGC	ACT
rs2304715	CCGCCTGGCACGGCGGA	ACT
rs2301272	TGTGCTAGGACAAGATCCTAGCT	ACT
rs2301273	GCTGACTTACGGTAAAGCGG	ACT
rs3784563	TGACCACAATTTATGCTGCCA	ACT
rs3784561	GCAGGTGGATAGTAAGTTTCCA	ACT

dbSNP rs#	Extend Primer	Term Mix
rs3784561	GCTGGATTCTAGGATCAGAGACA	ACT
rs3784560	CTAGGATCAGAGACAGGTAG	ACT

Genetic Analysis

[0307] Allelotyping results from the discovery cohort are shown for cases and controls in Table 51. The allele frequency for the A2 allele is noted in the fifth and sixth columns for osteoarthritis case pools and control pools, respectively, where “AF” is allele frequency. The allele frequency for the A1 allele can be easily calculated by subtracting the A2 allele frequency from 1 (A1 AF = 1-A2 AF). For example, the SNP rs1048661 has the following case and control allele frequencies: case A1 (G) = 0.725; case A2 (T) = 0.275; control A1 (G) = 0.767; and control A2 (T) = 0.233, where the nucleotide is provided in paranthesis. Some SNPs are labeled “untyped” because of failed assays.

TABLE 51

dbSNP rs#	Position in SEQ ID NO: 10	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1048661	213	71935363	G/T	0.275	0.233	0.077
rs3825942	249	71935399	C/T	0.107	0.148	0.056
rs1550436	1824	71936974	C/T	0.401	0.420	0.470
rs1550438	2057	71937207	C/T			
rs1550439	2306	71937456	A/T			
rs2165241	2869	71938019	C/T	0.427	0.430	0.883
rs1550433	3976	71939126	A/C			
rs3056314	4288	71939438	-/TC			
rs2415204	4290	71939440	A/C	0.176	0.177	0.982
rs1992314	4434	71939584	C/G	0.599	0.601	0.938
rs1440101	5298	71940448	A/G			
rs2289414	5467	71940617	A/G			
rs2415205	8486	71943636	C/G			
rs2899807	8487	71943637	A/T	0.951	0.956	0.863
rs893815	8831	71943981	C/G			
rs3056342	9036	71944186	-/AG	0.290	0.292	0.927
rs4077284	9058	71944208	A/G	0.358	0.358	0.985
rs893816	9131	71944281	C/T	0.517	0.515	0.928
rs893817	9732	71944882	A/G	0.162	0.158	0.819
rs893818	9862	71945012	A/G	0.311	0.313	0.920
rs893819	10191	71945341	A/G	0.637	0.642	0.866
rs893820	10270	71945420	C/T	0.901	0.910	0.605
rs2304719	16167	71951317	C/T	0.320	0.299	0.387
rs1001507	17620	71952770	G/T	0.910	0.916	0.709
rs1530167	17751	71952901	C/T			
rs1530168	17764	71952914	C/T			
rs1530169	17787	71952937	C/T	0.209	0.203	0.779
rs2304720	19401	71954551	C/T	0.942	0.947	0.724
rs2304721	21021	71956171	A/C	0.798	0.814	0.519
rs893821	21902	71957052	C/T	0.113	0.116	0.879
rs750460	22173	71957323	C/T	0.473	0.438	0.176
rs2304722	22416	71957566	C/T	0.744	0.747	0.926
rs1440102	22653	71957803	A/G			
rs8818	24945	71960095	C/G			
rs3522	25011	71960161	C/T	0.424	0.441	0.472
rs2415206	28563	71963713	C/T	0.376	0.366	0.731
rs1984526	48574	71983724	C/G	0.593	untyped	NA
rs1984525	48710	71983860	C/T			
rs3031653	48880	71984030	-/TTG			

dbSNP rs#	Position in SEQ ID NO: 10	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs2415187	50194	71985344	C/T			
rs2507	56343	71991493	A/G	0.655	0.653	0.924
rs2289411	56455	71991605	C/T			
rs3202077	56729	71991879	C/T			
rs2289412	56759	71991909	A/G	0.971	0.968	0.855
rs2289413	56895	71992045	A/G	0.972	0.972	0.997
rs1061082	57036	71992186	C/G			
rs2277600	57702	71992852	C/G			
rs734854	62515	71997665	C/T	0.381	0.379	0.915
rs2415188	62629	71997779	C/G	0.532	0.538	0.832
rs3214695	63501	71998651	-/C	0.308	0.300	0.751
rs3816197	63547	71998697	C/T	0.327	0.311	0.512
rs3816198	64876	72000026	C/G	0.598	0.584	0.575
rs2304715	65073	72000223	C/G	0.660	0.643	0.534
rs2301272	67149	72002299	C/T	0.974	0.972	0.853
rs2301273	67549	72002699	C/T	0.952	0.966	0.409
rs3784563	71660	72006810	A/C	0.495	0.508	0.590
rs3784561	71906	72007056	C/T	0.470	0.466	0.872
rs3784560	71911	72007061	A/C			

[0308] The *LOXL1* proximal SNPs were also allelotyped in the replication cohorts using the methods described herein and the primers provided in Tables 49 and 50. The replication allelotyping results for replication cohort #1 and replication cohort #2 are provided in Tables 52 and 53, respectively.

TABLE 52

dbSNP rs#	Position in SEQ ID NO: 10	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1048661	213	71935363	G/T	0.250	0.252	0.953
rs3825942	249	71935399	C/T	0.126	0.141	0.539
rs1550436	1824	71936974	C/T	0.397	0.405	0.845
rs1550438	2057	71937207	C/T			
rs1550439	2306	71937456	A/T			
rs2165241	2869	71938019	C/T	0.429	0.425	0.894
rs1550433	3976	71939126	A/C			
rs3056314	4288	71939438	-/T/C			
rs2415204	4290	71939440	A/C	0.162	untyped	0.176
rs1992314	4434	71939584	C/G	0.583	0.594	0.756
rs1440101	5298	71940448	A/G			
rs2289414	5467	71940617	A/G			
rs2415205	8486	71943636	C/G			
rs2899807	8487	71943637	A/T	0.939	untyped	NA
rs893815	8831	71943981	C/G			
rs3056342	9036	71944186	-/A/G	0.317	0.311	0.846
rs4077284	9058	71944208	A/G	0.372	0.365	0.881
rs893816	9131	71944281	C/T	0.510	0.518	0.793
rs893817	9732	71944882	A/G	0.178	0.170	0.784
rs893818	9862	71945012	A/G	0.327	0.320	0.818
rs893819	10191	71945341	A/G	0.610	untyped	NA
rs893820	10270	71945420	C/T	0.874	0.903	0.218
rs2304719	16167	71951317	C/T	0.309	0.289	0.537
rs1001507	17620	71952770	G/T	0.908	0.924	0.525
rs1530167	17751	71952901	C/T			
rs1530168	17764	71952914	C/T			
rs1530169	17787	71952937	C/T	0.237	0.202	0.249
rs2304720	19401	71954551	C/T	0.935	0.944	0.661
rs2304721	21021	71956171	A/C	0.759	0.823	0.091
rs893821	21902	71957052	C/T	0.114	0.122	0.778

dbSNP rs#	Position in SEQ ID NO: 10	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs750460	22173	71957323	C/T	0.469	0.440	0.433
rs2304722	22416	71957566	C/T	0.729	0.746	0.572
rs1440102	22653	71957803	A/G			
rs8818	24945	71960095	C/G			
rs3522	25011	71960161	C/T	0.416	0.440	0.454
rs2415206	28563	71963713	C/T	0.362	untyped	NA
rs1984526	48574	71983724	C/G	0.593	untyped	
rs1984525	48710	71983860	C/T			
rs3031653	48880	71984030	-/TTG			
rs2415187	50194	71985344	C/T			
rs2507	56343	71991493	A/G	0.676	0.653	0.471
rs2289411	56455	71991605	C/T			
rs3202077	56729	71991879	C/T			
rs2289412	56759	71991909	A/G	0.964	0.954	0.626
rs2289413	56895	71992045	A/G	0.963	0.959	0.833
rs1061082	57036	71992186	C/G			
rs2277600	57702	71992852	C/G			
rs734854	62515	71997665	C/T	0.403	0.383	0.531
rs2415188	62629	71997779	C/G	0.555	0.564	0.809
rs3214695	63501	71998651	-/C	0.289	0.300	0.721
rs3816197	63547	71998697	C/T	0.304	0.308	0.904
rs3816198	64876	72000026	C/G	0.601	0.598	0.922
rs2304715	65073	72000223	C/G	0.649	0.678	0.457
rs2301272	67149	72002299	C/T	0.966	0.959	0.752
rs2301273	67549	72002699	C/T	0.935	0.946	0.649
rs3784563	71660	72006810	A/C	0.502	0.516	0.685
rs3784561	71906	72007056	C/T	0.438	0.471	0.319
rs3784560	71911	72007061	A/C			

TABLE 53

dbSNP rs#	Position in SEQ ID NO: 10	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1048661	213	71935363	G/T	0.307	0.203	0.007
rs3825942	249	71935399	C/T	0.084	0.159	0.031
rs1550436	1824	71936974	C/T	0.406	0.445	0.274
rs1550438	2057	71937207	C/T			
rs1550439	2306	71937456	A/T			
rs2165241	2869	71938019	C/T	0.423	0.439	0.669
rs1550433	3976	71939126	A/C			
rs3056314	4288	71939438	-/TC			
rs2415204	4290	71939440	A/C	0.200	untyped	
rs1992314	4434	71939584	C/G	0.618	0.612	0.854
rs1440101	5298	71940448	A/G			
rs2289414	5467	71940617	A/G			
rs2415205	8486	71943636	C/G			
rs2899807	8487	71943637	A/T	0.965	0.956	0.737
rs893815	8831	71943981	C/G			
rs3056342	9036	71944186	-/AG	0.257	0.264	0.833
rs4077284	9058	71944208	A/G	0.341	0.345	0.905
rs893816	9131	71944281	C/T	0.526	0.509	0.655
rs893817	9732	71944882	A/G	0.142	0.139	0.895
rs893818	9862	71945012	A/G	0.290	0.302	0.712
rs893819	10191	71945341	A/G	0.671	0.642	0.431
rs893820	10270	71945420	C/T	0.934	0.922	0.681
rs2304719	16167	71951317	C/T	0.334	0.316	0.613
rs1001507	17620	71952770	G/T	0.911	0.903	0.741
rs1530167	17751	71952901	C/T			
rs1530168	17764	71952914	C/T			
rs1530169	17787	71952937	C/T	0.173	0.203	0.360
rs2304720	19401	71954551	C/T	0.951	0.952	0.952
rs2304721	21021	71956171	A/C	0.848	0.799	0.150

dbSNP rs#	Position in SEQ ID NO: 10	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs893821	219 02	71957052	C/T	0.112	0.106	0.829
rs750460	221 73	71957323	C/T	0.478	0.435	0.242
rs2304722	224 16	71957566	C/T	0.764	0.748	0.626
rs1440102	226 53	71957803	A/G			
rs8818	249 45	71960095	C/G			
rs3522	250 11	71960161	C/T	0.435	0.444	0.814
rs2415206	285 63	71963713	C/T	0.394	0.366	0.419
rs1984526	485 74	71983724	C/G			
rs1984525	487 10	71983860	C/T			
rs3031653	488 80	71984030	-/TTG			
rs2415187	501 94	71985344	C/T			
rs2507	563 43	71991493	A/G	0.630	0.653	0.509
rs2289411	564 55	71991605	C/T			
rs3202077	567 29	71991879	C/T			
rs2289412	567 59	71991909	A/G	0.979	untyped	
rs2289413	568 95	71992045	A/G			
rs1061082	570 36	71992186	C/G			
rs2277600	577 02	71992852	C/G			
rs734854	625 15	71997665	C/T	0.354	0.372	0.611
rs2415188	626 29	71997779	C/G	0.502	0.497	0.897
rs3214695	635 01	71998651	-/C	0.331	0.300	0.367
rs3816197	635 47	71998697	C/T	0.357	0.317	0.259
rs3816198	648 76	72000026	C/G	0.594	0.562	0.416
rs2304715	650 73	72000223	C/G	0.674	0.587	0.020
rs2301272	671 49	72002299	C/T			
rs2301273	675 49	72002699	C/T	0.973	untyped	
rs3784563	716 60	72006810	A/C	0.485	0.496	0.777
rs3784561	719 06	72007056	C/T	0.511	0.459	0.174
rs3784560	719 11	72007061	A/C			

[0309] Allelotyping results were considered particularly significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The allelotyping p-values were plotted in Figure 1H for the discovery cohort. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figure 1E can be determined by consulting Table 51. For example, the left-most X on the left graph is at position 71935363. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0310] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The generally bottom-most curve is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square

goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0311] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is placed at the 3' end of each gene to show the direction of transcription.

Example 12

CASPR4 Region Proximal SNPs

[0312] It has been discovered that rs1395486 in the cell recognition protein *CASPR4* gene is associated with occurrence of osteoarthritis in subjects. This gene product belongs to the neurexin family, members of which function in the nervous system as cell adhesion molecules and receptors. Like other neurexin proteins, *CASPR4* contains epidermal growth factor repeats and laminin G domains. In addition, it includes an F5/8 type C domain, discoidin/neuropilin- and fibrinogen-like domains, and thrombospondin N-terminal-like domains. Alternative splicing of this gene results in 2 transcript variants encoding different isoforms. *CASPR4* biological activity can be modulated by addition of an antibody, a recombinant binding partner, a binding agent, or a recombinant *CASPR4* protein or functional fragment thereof.

[0313] Fifty-six additional allelic variants proximal to rs1395486 were identified and subsequently allelotyped in osteoarthritis case and control sample sets as described in Examples 1 and 2. The polymorphic variants are set forth in Table 54. The chromosome positions provided in column four of Table 54 are based on Genome "Build 34" of NCBI's GenBank.

TABLE 54

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 11	Chromosome Position	Allele Variants
rs1896753	16	205	76177855	C/T
rs3974451	16	866	76178516	C/T
rs1820770	16	4212	76181862	C/T
rs1428753	16	5934	76183584	C/T
rs722229	16	11486	76189136	C/T
rs3851754	16	16969	76194619	A/G
rs2340430	16	22509	76200159	A/G
rs2340431	16	22796	76200446	A/G
rs1159415	16	28097	76205747	C/T
rs1506836	16	28626	76206276	C/T
rs1506837	16	28853	76206503	C/T
rs1506838	16	28873	76206523	C/T
rs966668	16	30155	76207805	A/G
rs1911245	16	30827	76208477	C/T
rs1506839	16	31956	76209606	C/T
rs1506840	16	32404	76210054	C/T

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 11	Chromosome Position	Allele Variants
rs1876275	16	32944	76210594	A/G
rs1911242	16	35205	76212855	A/G
rs1911243	16	35227	76212877	C/T
rs981231	16	35781	76213431	C/T
rs1506829	16	41052	76218702	C/T
rs1506833	16	45051	76222701	A/G
rs1395486	16	46039	76223689	C/T
rs1506832	16	47276	76224926	A/G
rs1506830	16	47678	76225328	C/T
rs968537	16	47716	76225366	A/G
rs1506816	16	51014	76228664	A/G
rs1506828	16	54408	76232058	A/G
rs1506827	16	54596	76232246	C/T
rs1542969	16	56853	76234503	C/G
rs1395484	16	61851	76239501	A/G
rs1876274	16	62016	76239666	A/G
rs1876273	16	62461	76240111	C/T
rs1506822	16	68257	76245907	C/G
rs1506820	16	69793	76247443	C/T
rs1506819	16	73976	76251626	A/C
rs1506818	16	73999	76251649	A/T
rs1506817	16	74053	76251703	A/G
rs1395488	16	75315	76252965	A/G
rs2221534	16	75729	76253379	G/T
rs1911244	16	76466	76254116	A/G
rs2135624	16	77216	76254866	C/T
rs2135623	16	77217	76254867	G/T
rs1506835	16	79239	76256889	C/G
rs1506834	16	80825	76258475	A/G
rs1995653	16	81060	76258710	C/G
rs1995652	16	81097	76258747	A/C
rs1395487	16	81426	76259076	G/T
rs3947083	16	84787	76262437	C/T
rs1506825	16	84896	76262546	A/T
rs1506824	16	85165	76262815	C/G
rs1567118	16	86502	76264152	C/G
rs1039683	16	86753	76264403	C/T
rs2879777	16	86941	76264591	C/T
rs1876272	16	88787	76266437	C/T
rs3035878	16	95598	76273248	-/AGAGC

Assay for Verifying and Allelotyping SNPs

[0314] The methods used to verify and allelotype the 56 proximal SNPs of Table 54 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 55 and Table 56, respectively.

TABLE 55

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs1896753	ACGTTGGATGTTTG AAGAGAGGGACTAGAG	ACGTTGGATGGAAAATGAACTGG AATGGGG
rs3974451	ACGTTGGATGTTGC ATAAGGTGTGAGGAAG	ACGTTGGATGAATGGTGTGGGAA AACTGG
rs1820770	ACGTTGGATGCTTG GAACCAACCCAAATGC	ACGTTGGATGGGCTGCATAGTAT TCCACAG
rs1428753	ACGTTGGATGCAATAGCTATCTCCTACTTG	ACGTTGGATGGATGCTTTGTATTGACAACC
rs722229	ACGTTGGATGGAAGGAGGCTCACTATTTCC	ACGTTGGATGGGCTAGGGTAGCA AACATCA
rs3851754	ACGTTGGATGAGGTTTGGAGAATGCCAACT	ACGTTGGATGAGATTGAATCAGATGGACTG
rs2340430	ACGTTGGATGATGCGCTTCCAAAGATGTTT	ACGTTGGATGCATCTACAATCCCA ATATGCC
rs2340431	ACGTTGGATGTTTG TGCAACCTCTGCAAGC	ACGTTGGATGAGATGTCAGCAGGATGCATG
rs1159415	ACGTTGGATGGCTTTC CAATGATTGTTGGAG	ACGTTGGATGCTGGGTCTTCCTAATGTGTT
rs1506836	ACGTTGGATGCCTGGGCACAGATTCATTTT	ACGTTGGATGCTGCAGCGACCTTTCATTCA
rs1506837	ACGTTGGATGCTGACATTGAGCTAGTCTTTC	ACGTTGGATGGTAGTTGGTGAATTTGGTGG
rs1506838	ACGTTGGATGGTAGTTGGTGAATTTGGTGG	ACGTTGGATGGACATTGAGCTAGTCTTTTCC
rs966668	ACGTTGGATGCACTTCATAGTGTGAAAAGTC	ACGTTGGATGCCAGTAAATGCAAGATTTTCC
rs1911245	ACGTTGGATGAACA ACTAGGCAATTCGGTG	ACGTTGGATGCCATCAGAAGTAAACCGTTTC
rs1506839	ACGTTGGATGCCAAATTTTGCTTTGTTAGAC	ACGTTGGATGTGCACAATTCAAGTGAAGTC
rs1506840	ACGTTGGATGGGAAGAATGACCTTGTGTGG	ACGTTGGATGAGCTGTGAGTGAGGATGATG
rs1876275	ACGTTGGATGAAC TGTTCTCTGCCCTTTGG	ACGTTGGATGTTACGGACATAAGGGAAGG
rs1911242	ACGTTGGATGGTTC CCTAAGTACTTTAGAA	ACGTTGGATGCTCTGCAAAGCAATAAGCTAC
rs1911243	ACGTTGGATGCTTA TAATTCAGTTCCTAAG	ACGTTGGATGGCAATAAGCTACC AAAATAG
rs981231	ACGTTGGATGATGCTAACCTGTCTAAATCC	ACGTTGGATGTAGTGCTCTGGAC TAGAAAG
rs1506829	ACGTTGGATGTGGAAAGTTGCAATTCCTTG	ACGTTGGATGCCATCTTAAACCATGCGAG
rs1506833	ACGTTGGATGGTTT TATCTGGTTCCTTACAG	ACGTTGGATGGCTGTATACGTAC TTTAAAC
rs1395486	ACGTTGGATGCTCATTATTTTCATGTTTAC	ACGTTGGATGTGCTGGAATAATGATTGTTG
rs1506832	ACGTTGGATGGGTAATGGTCATAAGAATGCC	ACGTTGGATGGAGCTCAATTAGCATCTCTC
rs1506830	ACGTTGGATGCAACAGTAAAGGCATGAAAG	ACGTTGGATGCATTGGACTATCAAAAAGTG
rs968537	ACGTTGGATGATTA TTTGGTGGGAAGAGGG	ACGTTGGATGAAATGTTACGTAGGCCAAAC
rs1506816	ACGTTGGATGTACATATGACCACTGTTTCC	ACGTTGGATGCTAAGCAGGGAAGTAGTAAG
rs1506828	ACGTTGGATGGAGCTTTTCCATTAGACCC	ACGTTGGATGGTTGAAAATCAGACAAGGGC
rs1506827	ACGTTGGATGAATGCGCTATATCTGATGAC	ACGTTGGATGAACCCATTTCTTAGCCAGAG
rs1542969	ACGTTGGATGCAGATTACAGCCAAGTTTGC	ACGTTGGATGGGTTTGAATTTCC AAGACAG
rs1395484	ACGTTGGATGCAAGCTCACATAACACAGGC	ACGTTGGATGAAGAGATGCCCGATTTTGG
rs1876274	ACGTTGGATGGGTATCTGATCATCTGCCTG	ACGTTGGATGGGGATTGATTGACAAGGAG
rs1876273	ACGTTGGATGTGGAAGAAACATAGCTCCTG	ACGTTGGATGAAAATCCCTCCAGTGTTTGC
rs1506822	ACGTTGGATGTTCTCCAGATCTGCAAACAG	ACGTTGGATGGTAATGAGAGAAGTAGAGGC
rs1506820	ACGTTGGATGTTCTATATATGTGTGTGTGC	ACGTTGGATGTTAGGGTCTCTAGAAAGAC
rs1506819	ACGTTGGATGTGAGGGAATTGTGTCTGCAG	ACGTTGGATGGCCAGAGAGGCTAGAAATTG
rs1506818	ACGTTGGATGAGGCTGCTTAGCATTTTAC	ACGTTGGATGAGATCAGAGAGCAATGGTCC
rs1506817	ACGTTGGATGCCTCTTTCTCGTGCTTTCTC	ACGTTGGATGCTCAGATCCTTGGCCAATTC
rs1395488	ACGTTGGATGGACA CTTGAATGCATACCG	ACGTTGGATGGGTGACTTCTGTGACATTGC
rs2221534	ACGTTGGATGTAATGCAGGTCTCAAGTGCC	ACGTTGGATGCAAATCAGACTGAGTCGCTG
rs1911244	ACGTTGGATGACCTGTATTCCTGTTCCAGG	ACGTTGGATGCAACATTCTACTTCCTGGGC
rs2135624	ACGTTGGATGGTACGCCCTACTCTCATATC	ACGTTGGATGAGCTCTTAATTCCATGGCAG
rs2135623	ACGTTGGATGGTACGCCCTACTCTCATATC	ACGTTGGATGAGCTCTTAATTCCATGGCAG
rs1506835	ACGTTGGATGAATTAGCTGGACATGGTGGC	ACGTTGGATGTCAAGTGAACCTCAACCTC
rs1506834	ACGTTGGATGACATTTTCCAGCACTGTCC	ACGTTGGATGCTCACTCCTACTCTGAGTAC
rs1995653	ACGTTGGATGCCAGCCTTCTGTTACTCTTG	ACGTTGGATGCTGTCCTCATGGTGTTCCTCA
rs1995652	ACGTTGGATGCGTGTTACAACCTGTAATGC	ACGTTGGATGACATAAATATGGCCTCTGTC
rs1395487	ACGTTGGATGAAAAGCTTTAGGTGCCACAG	ACGTTGGATGGCTTGTGTTACTTTAGCTAC
rs3947083	ACGTTGGATGAAGTGGGCTCTTTATAGTG	ACGTTGGATGGAGGTGTGATGGTTATGTTTC
rs1506825	ACGTTGGATGCCTGCATATGATGTTCTGTG	ACGTTGGATGTAGCAGCTTTCGGTGTATAG

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs1506824	ACGTTGGATGAGCAATGGATTCAAA TGCTC	ACGTTGGATGCACTGGTCGATGAAAAATAC
rs1567118	ACGTTGGATGTCGGCCAATCTGTCC AATG	ACGTTGGATGAATTGTCCCCGTTTCCACAG
rs1039683	ACGTTGGATGTGATGTGTGGAGGCA TGTTG	ACGTTGGATGACAGGCAACAAC TGCCAAAG
rs2879777	ACGTTGGATGCTAATCATGTGCGAT GAGGG	ACGTTGGATGAAGAAGAGATGGGCCATAGT
rs1876272	ACGTTGGATGTTCTTTGTCTGGAGT GGGAG	ACGTTGGATGGGTTCCAACACTAGCAGTT C
rs3035878	ACGTTGGATGTTCTACAAGGAGCTG TGTAG	ACGTTGGATGCTGACTGGTAAATTCACGAC

TABLE 56

dbSNP rs#	Extend Primer	Term Mix
rs1896753	GGAATTT AATTTGGTGCCTCTTCA	ACT
rs3974451	TTCAGT TTCAGCTTTCTGCATA	ACG
rs1820770	GAACCA ACCCAAATGCCCATCA	ACT
rs1428753	TAACATT TACTGATAGAATAAAGC	ACT
rs722229	TTCCTT GCAGAAAATGAGACA	ACT
rs3851754	AACTCA CACACACACACAGAA	ACT
rs2340430	CGTTG GGACCTATAGGTATG	ACT
rs2340431	CTCTG CAAGCTGGAAAGGAC	ACT
rs1159415	TATGTTT AGGAACATTTTCCTAAC	ACT
rs1506836	GTCTC ACAGCTTGAAGATGC	ACG
rs1506837	CATTGAGCTAGTCTTTCCTCTGT	ACG
rs1506838	GTTGGTG AATTTGGTGGAGAATCT	ACT
rs966668	TCATAGT GTGAAAAGTCTAAAAAA	ACT
rs1911245	TTCCTC TTTTTCAGACAAAATTG	ACG
rs1506839	AATTTTG CTTTGTTAGACCTTAGG	ACG
rs1506840	GCTGG TGTCTGTGAAATTG	ACG
rs1876275	TCTTG GTTCAGGTATCACCTA	ACG
rs1911242	TAGAAAA ATTTGCCTTTTGAGAAA	ACG
rs1911243	TAATTCA GTTCCCTAAGTACTTTA	ACT
rs981231	CCTGTCT AAATCCATTTGATTAAA	ACT
rs1506829	GATCTA AATAGCTACTGGGAAA	ACT
rs1506833	TCTGGTT CCTTACAGAAACACTTA	ACG
rs1395486	TTTCATG TTCACAAAAAATCTTCT	ACG
rs1506832	GGTCAT AAGAATGCCATTATTCT	ACG
rs1506830	AATAATA TGTTTGGCCTACGTAA	ACG
rs968537	AGGGAG GTAAGAGTCAACAGTAA	ACT
rs1506816	ATATGACCACTGTTTCCTCATTT	ACT
rs1506828	CCATTAGACCCCTTAGCATAT	ACG
rs1506827	TGACAAT AGAACTAAGACAAATA	ACT
rs1542969	GCCAAGTTTGCATCTTTCATGT	ACT
rs1395484	AACAC AGGCACAGCTGTGAT	ACT
rs1876274	CTAATTC ACAAAATATTCCCTTACT	ACT
rs1876273	TAGCT CCTGGCCCTACCAT	ACT
rs1506822	CTGCA AACAGGATCACTGCT	ACT
rs1506820	ATATAC AGAACACACACACACA	ACG
rs1506819	TCTGCAGGAGCACGGACC	CGT
rs1506818	GGCCAAGGATCTGAGGGAA	CGT

dbSNP rs#	Extend Primer	Term Mix
rs1506817	TGCTTTCTC TAGGGCTGCTT	ACT
rs1395488	TGAATGCAT CACCGGAGGAT	ACT
rs2221534	CTCAAGTGC CTATCTATCATG	CGT
rs1911244	TTCCAGGTTAGAATTCCAGAGAT	ACG
rs2135624	CTCTCATATCAATTCTCCCTGTT	ACG
rs2135623	CTCTCATATCAATTCTCCCTGT	ACT
rs1506835	GACATGGTGGCAAATTCCTGTA	ACT
rs1506834	ACTGTCCCATTCACTGTCATAA	ACT
rs1995653	TTCTGTTACTC TTGATCAGAATGC	ACT
rs1995652	TAATGCTTTTA TGAACCTAGTTGT	ACT
rs1395487	CTTTAGGTGCCACAGAAGATA	CGT
rs3947083	GGGCTCTTTATAGTGTATTTTCCT	ACG
rs1506825	ATACTGTGAGAAAGATGAAGGT	CGT
rs1506824	CAAATGCTCAAATATCAATATGTG	ACT
rs1567118	TGTCCAAATGGCAATGTTGGT	ACT
rs1039683	GGAGGCATGTTGGAACCTACAGAC	ACT
rs2879777	GAGGGGTGGTCACACAGC	ACT
rs1876272	CTGGAGTGGGAGACAGGGT	ACG
rs3035878	TGTGTAGCTAAATGTTGAGCAGAG	ACT

Genetic Analysis

[0315] Allelotyping results from the discovery cohort are shown for cases and controls in Table 57. The allele frequency for the A2 allele is noted in the fifth and sixth columns for osteoarthritis case pools and control pools, respectively, where “AF” is allele frequency. The allele frequency for the A1 allele can be easily calculated by subtracting the A2 allele frequency from 1 (A1 AF = 1-A2 AF). For example, the SNP rs1896753 has the following case and control allele frequencies: case A1 (A) = 0.79; case A2 (T) = 0.21; control A1 (A) = 0.81; and control A2 (T) = 0.19, where the nucleotide is provided in paranthesis. Some SNPs are labeled “untyped” because of failed assays.

TABLE 57

dbSNP rs#	Position in SEQ ID NO: 11	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1896753	205	76177855	C/T			
rs3974451	866	76178516	C/T			
rs1820770	4212	76181862	C/T			
rs1428753	5934	76183584	C/T	0.486	0.467	0.459
rs722229	11486	76189136	C/T			
rs3851754	16969	76194619	A/G	0.287	0.300	0.569
rs2340430	22509	76200159	A/G	0.488	0.523	0.155
rs2340431	22796	76200446	A/G	0.030	0.028	0.844
rs1159415	28097	76205747	C/T	0.480	0.477	0.919
rs1506836	28626	76206276	C/T	0.401	0.404	0.891
rs1506837	28853	76206503	C/T	0.394	0.396	0.933
rs1506838	28873	76206523	C/T	0.334	0.343	0.727
rs966668	30155	76207805	A/G			
rs1911245	30827	76208477	C/T	0.836	0.824	0.631
rs1506839	31956	76209606	C/T	0.434	0.436	0.936
rs1506840	32404	76210054	C/T	0.382	0.381	0.993

dbSNP rs#	Position in SEQ ID NO: 11	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1876275	32944	76210594	A/G	0.463	0.461	0.918
rs1911242	35205	76212855	A/G	0.419	0.410	0.703
rs1911243	35227	76212877	C/T			
rs981231	35781	76213431	C/T	0.451	0.430	0.510
rs1506829	41052	76218702	C/T	0.393	0.379	0.576
rs1506833	45051	76222701	A/G	0.509	0.530	0.378
rs1395486	46039	76223689	C/T			
rs1506832	47276	76224926	A/G	0.518	0.516	0.949
rs1506830	47678	76225328	C/T	0.036	0.031	0.710
rs968537	47716	76225366	A/G	0.243	0.275	0.175
rs1506816	51014	76228664	A/G	0.392	0.369	0.348
rs1506828	54408	76232058	A/G	0.418	0.413	0.816
rs1506827	54596	76232246	C/T	0.432	0.449	0.477
rs1542969	56853	76234503	C/G			
rs1395484	61851	76239501	A/G	0.417	0.441	0.349
rs1876274	62016	76239666	A/G	0.381	0.369	0.629
rs1876273	62461	76240111	C/T	0.382	0.364	0.445
rs1506822	68257	76245907	C/G	0.355	0.351	0.855
rs1506820	69793	76247443	C/T	0.326	0.256	0.054
rs1506819	73976	76251626	A/C	0.446	0.424	0.358
rs1506818	73999	76251649	A/T	0.126	0.145	0.465
rs1506817	74053	76251703	A/G	0.186	0.199	0.570
rs1395488	75315	76252965	A/G	0.489	0.499	0.689
rs2221534	75729	76253379	G/T	0.450	0.431	0.455
rs1911244	76466	76254116	A/G	0.493	0.491	0.960
rs2135624	77216	76254866	C/T			
rs2135623	77217	76254867	G/T	0.034	0.032	0.899
rs1506835	79239	76256889	C/G	0.549	0.538	0.666
rs1506834	80825	76258475	A/G	0.390	0.392	0.958
rs1995653	81060	76258710	C/G	0.396	0.402	0.783
rs1995652	81097	76258747	A/C	0.436	0.435	0.979
rs1395487	81426	76259076	G/T	0.505	0.504	0.975
rs3947083	84787	76262437	C/T	0.373	0.366	0.773
rs1506825	84896	76262546	A/T	0.412	0.398	0.569
rs1506824	85165	76262815	C/G	0.444	0.414	0.242
rs1567118	86502	76264152	C/G	0.032	0.024	0.557
rs1039683	86753	76264403	C/T	0.382	0.373	0.707
rs2879777	86941	76264591	C/T	0.269	0.279	0.676
rs1876272	88787	76266437	C/T			
rs3035878	95598	76273248	-/AGAGC	0.978	untyped	NA

[0316] The *CASPR4* proximal SNPs were also allelotyped in the replication cohorts using the methods described herein and the primers provided in Tables 55 and 56. The replication allelotyping results for replication cohort #1 and replication cohort #2 are provided in Tables 58 and 59, respectively.

TABLE 58

dbSNP rs#	Position in SEQ ID NO: 11	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1896753	205	76177855	C/T			
rs3974451	866	76178516	C/T			
rs1820770	4212	76181862	C/T			
rs1428753	5934	76183584	C/T	0.463	0.474	0.756
rs722229	11486	76189136	C/T			
rs3851754	16969	76194619	A/G	0.283	0.309	0.375
rs2340430	22509	76200159	A/G	0.494	0.519	0.477
rs2340431	22796	76200446	A/G	0.035	0.028	0.748
rs1159415	28097	76205747	C/T	0.436	0.472	0.287

dbSNP rs#	Position in SEQ ID NO: 11	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1506836	28626	76206276	C/T	0.392	0.401	0.786
rs1506837	28853	76206503	C/T	0.388	0.399	0.727
rs1506838	28873	76206523	C/T	0.318	0.327	0.778
rs966668	30155	76207805	A/G			
rs1911245	30827	76208477	C/T	0.825	0.821	0.896
rs1506839	31956	76209606	C/T	0.450	0.441	0.817
rs1506840	32404	76210054	C/T	0.379	0.383	0.926
rs1876275	32944	76210594	A/G	0.469	0.470	0.986
rs1911242	35205	76212855	A/G	0.437	0.415	0.514
rs1911243	35227	76212877	C/T			
rs981231	35781	76213431	C/T	0.449	0.414	0.415
rs1506829	41052	76218702	C/T	0.398	0.394	0.894
rs1506833	45051	76222701	A/G	0.515	0.544	0.393
rs1395486	46039	76223689	C/T			
rs1506832	47276	76224926	A/G	0.526	0.511	0.720
rs1506830	47678	76225328	C/T	0.053	0.039	0.488
rs968537	47716	76225366	A/G	0.241	0.298	0.045
rs1506816	51014	76228664	A/G	0.379	0.370	0.771
rs1506828	54408	76232058	A/G	0.416	0.429	0.706
rs1506827	54596	76232246	C/T	0.428	0.435	0.836
rs1542969	56853	76234503	C/G			
rs1395484	61851	76239501	A/G	0.418	0.459	0.208
rs1876274	62016	76239666	A/G	0.384	0.382	0.942
rs1876273	62461	76240111	C/T	0.393	0.360	0.271
rs1506822	68257	76245907	C/G	0.353	0.368	0.637
rs1506820	69793	76247443	C/T	0.288	untyped	NA
rs1506819	73976	76251626	A/C	0.453	0.424	0.378
rs1506818	73999	76251649	A/T	0.149	NA	0.126
rs1506817	74053	76251703	A/G	0.195	0.212	0.573
rs1395488	75315	76252965	A/G	0.490	0.490	1.000
rs2221534	75729	76253379	G/T	0.446	0.433	0.711
rs1911244	76466	76254116	A/G	0.495	0.480	0.646
rs2135624	77216	76254866	C/T			
rs2135623	77217	76254867	G/T	0.027	0.030	0.896
rs1506835	79239	76256889	C/G	0.563	0.556	0.848
rs1506834	80825	76258475	A/G	0.377	0.388	0.722
rs1995653	81060	76258710	C/G	0.381	0.395	0.675
rs1995652	81097	76258747	A/C	0.435	0.423	0.750
rs1395487	81426	76259076	G/T	0.505	0.500	0.874
rs3947083	84787	76262437	C/T	0.367	0.370	0.929
rs1506825	84896	76262546	A/T	0.406	0.397	0.798
rs1506824	85165	76262815	C/G	0.446	0.413	0.361
rs1567118	86502	76264152	C/G	0.029	0.023	0.776
rs1039683	86753	76264403	C/T	0.376	0.365	0.729
rs2879777	86941	76264591	C/T	0.265	0.278	0.669
rs1876272	88787	76266437	C/T			
rs3035878	95598	76273248	- /AGAGC	0.972	untyped	NA

TABLE 59

dbSNP rs#	Position in SEQ ID NO: 11	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1896753	205	76177855	C/T			
rs3974451	866	76178516	C/T			
rs1820770	4212	76181862	C/T			
rs1428753	5934	76183584	C/T	0.515	0.457	0.124
rs722229	11486	76189136	C/T			
rs3851754	16969	76194619	A/G	0.292	0.286	0.868
rs2340430	22509	76200159	A/G	0.480	0.531	0.169
rs2340431	22796	76200446	A/G	0.024	0.027	0.900
rs1159415	28097	76205747	C/T	0.535	0.485	0.252

dbSNP rs#	Position in SEQ ID NO: 11	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1506836	28626	76206276	C/T	0.412	0.410	0.947
rs1506837	28853	76206503	C/T	0.402	0.391	0.768
rs1506838	28873	76206523	C/T	0.355	0.368	0.734
rs966668	30155	76207805	A/G			
rs1911245	30827	76208477	C/T	0.849	0.828	0.569
rs1506839	31956	76209606	C/T	0.414	0.428	0.746
rs1506840	32404	76210054	C/T	0.384	0.379	0.905
rs1876275	32944	76210594	A/G	0.456	0.447	0.805
rs1911242	35205	76212855	A/G	0.397	0.402	0.892
rs1911243	35227	76212877	C/T			
rs981231	35781	76213431	C/T	0.454	0.455	0.971
rs1506829	41052	76218702	C/T	0.386	0.356	0.424
rs1506833	45051	76222701	A/G	0.500	0.509	0.811
rs1395486	46039	76223689	C/T			
rs1506832	47276	76224926	A/G	0.508	0.524	0.689
rs1506830	47678	76225328	C/T			
rs968537	47716	76225366	A/G	0.246	0.237	0.806
rs1506816	51014	76228664	A/G	0.408	0.367	0.284
rs1506828	54408	76232058	A/G	0.421	0.387	0.358
rs1506827	54596	76232246	C/T	0.436	0.471	0.346
rs1542969	56853	76234503	C/G			
rs1395484	61851	76239501	A/G	0.416	0.413	0.938
rs1876274	62016	76239666	A/G	0.376	0.350	0.447
rs1876273	62461	76240111	C/T	0.367	0.370	0.924
rs1506822	68257	76245907	C/G	0.358	0.325	0.355
rs1506820	69793	76247443	C/T	0.373	0.256	0.007
rs1506819	73976	76251626	A/C	0.438	0.424	0.703
rs1506818	73999	76251649	A/T	0.139	-0.013	
rs1506817	74053	76251703	A/G	0.174	0.178	0.897
rs1395488	75315	76252965	A/G	0.487	0.512	0.505
rs2221534	75729	76253379	G/T	0.455	0.429	0.463
rs1911244	76466	76254116	A/G	0.489	0.509	0.581
rs2135624	77216	76254866	C/T			
rs2135623	77217	76254867	G/T	0.042	0.035	0.748
rs1506835	79239	76256889	C/G	0.531	0.510	0.562
rs1506834	80825	76258475	A/G	0.407	0.397	0.787
rs1995653	81060	76258710	C/G	0.414	0.413	0.984
rs1995652	81097	76258747	A/C	0.437	0.455	0.629
rs1395487	81426	76259076	G/T	0.506	0.512	0.869
rs3947083	84787	76262437	C/T	0.379	0.359	0.559
rs1506825	84896	76262546	A/T	0.419	0.399	0.579
rs1506824	85165	76262815	C/G	0.442	0.414	0.471
rs1567118	86502	76264152	C/G	0.036	0.025	0.574
rs1039683	86753	76264403	C/T	0.389	0.385	0.910
rs2879777	86941	76264591	C/T	0.275	0.280	0.883
rs1876272	88787	76266437	C/T			
rs3035878	95598	76273248	- /AGAG C	untyped	0.980	NA

[0317] Allelotyping results were considered particularly significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The allelotyping p-values were plotted in Figure 1I for the discovery cohort. The position of each SNP on the chromosome is presented on the x-axis. The y-axis gives the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graphs in Figure 1I can be determined by consulting Table 57. For example, the left-most X on the left graph is at position

76177855. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0318] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The generally bottom-most curve is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0319] Finally, the exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is placed at the 3' end of each gene to show the direction of transcription.

Example 13

APOL3 Region Proximal SNPs

[0320] It has been discovered that SNP rs132659 in *APOL3* is associated with occurrence of osteoarthritis in subjects. *APOL3* belongs to the high density lipoprotein family that plays a central role in cholesterol transport. The cholesterol content of membranes is important in cellular processes such as modulating gene transcription and signal transduction both in the adult brain and during neurodevelopment. It has been shown that the APOL1-APOL4 gene cluster on chromosome 22 exists only in primates (humans and African green monkeys) and not in dogs, pigs, or rodents, suggesting that this gene cluster has arisen recently in evolution (Monajemi et. al., *Genomics* 79: 539-546, 2002). Six transcript variants encoding three different isoforms have been identified.

[0321] Expression of this gene is upregulated by tumor necrosis factor-alpha in endothelial cells lining the normal and atherosclerotic iliac artery and aorta (Horrevoets et. al., *Blood* 93: 3418-3431, 1999). *APOL3* is genetically linked to OA and may play a role in the pathophysiology of OA brought about by inflammation. *APOL3* is likely inhibited by a small molecule inhibitor or by specific antibodies. *APOL3* activity may be increased in a subject by administering *APOL3* recombinant protein or a functional fragment thereof.

[0322] Two hundred-nineteen additional allelic variants proximal to rs132659 were identified and subsequently allelotyped in osteoarthritis case and control sample sets as described in Examples 1 and 2.

The polymorphic variants are set forth in Table 60. The chromosome positions provided in column four of Table 60 are based on Genome "Build 34" of NCBI's GenBank.

TABLE 60

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 13	Chromosome Position	Allele Variants
rs3888818	22	201	34781551	c/t
rs2010605	22	425	34781775	a/g
rs743919	22	1095	34782445	g/t
rs1008134	22	2201	34783551	a/c
rs132607	22	7879	34789229	a/g
rs1476029	22	8395	34789745	c/t
rs1476030	22	8461	34789811	c/t
rs2413380	22	9503	34790853	c/t
rs2051609	22	10304	34791654	g/t
rs2413381	22	10695	34792045	c/t
rs1894604	22	16300	34797650	a/g
rs1894605	22	16444	34797794	g/t
rs132609	22	17591	34798941	c/t
rs132610	22	17988	34799338	-/a
rs132611	22	19116	34800466	-/t
rs132612	22	19358	34800708	c/t
rs1008790	22	20300	34801650	a/g
rs23085	22	20669	34802019	a/t
rs105161	22	20891	34802241	a/g
rs132613	22	21451	34802801	c/t
rs132614	22	21978	34803328	c/t
rs132615	22	22785	34804135	c/g
rs132617	22	24248	34805598	c/t
rs3865724	22	24770	34806120	c/t
rs2019657	22	24844	34806194	a/g
rs3865725	22	25066	34806416	g/t
rs2019364	22	25096	34806446	c/t
rs2008383	22	25309	34806659	a/g
rs3986002	22	25344	34806694	a/c
rs3888942	22	25529	34806879	a/t
rs3888943	22	25537	34806887	a/g
rs3888944	22	25554	34806904	a/c
rs132618	22	27963	34809313	a/t
rs132619	22	28134	34809484	g/t
rs3827346	22	28356	34809706	a/g
rs132620	22	29648	34810998	-/a
rs132621	22	29986	34811336	a/g
rs80575	22	30217	34811567	g/t
rs80576	22	30267	34811617	a/g
rs80577	22	30315	34811665	a/g
rs80578	22	30585	34811935	c/t
rs80579	22	30724	34812074	a/c
rs80580	22	30897	34812247	c/t
rs132622	22	30931	34812281	c/t
rs132623	22	31080	34812430	g/t
rs132624	22	31246	34812596	c/t
rs132625	22	31373	34812723	a/t

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 13	Chromosome Position	Allele Variants
rs132626	22	31463	34812813	a/g
rs132627	22	31467	34812817	a/g
rs1807672	22	32188	34813538	g/t
rs132628	22	32288	34813638	c/t
rs132629	22	32520	34813870	a/t
rs132630	22	32594	34813944	a/c
rs132631	22	32657	34814007	a/c
rs132632	22	32677	34814027	a/g
rs132633	22	32764	34814114	c/t
rs132634	22	32784	34814134	a/g
rs132635	22	32830	34814180	c/t
rs132636	22	32872	34814222	c/t
rs129603	22	33121	34814471	a/c
rs132637	22	33348	34814698	g/t
rs3788518	22	33952	34815302	c/g
rs132638	22	34184	34815534	c/g
rs132639	22	34361	34815711	a/t
rs132640	22	35026	34816376	a/g
rs132641	22	35192	34816542	a/g
rs132642	22	35600	34816950	a/t
rs132643	22	36033	34817383	c/t
rs132644	22	36289	34817639	c/t
rs132645	22	38869	34820219	a/g
rs2017329	22	39629	34820979	a/t
rs739198	22	40530	34821880	c/t
rs132647	22	41621	34822971	c/t
rs2097465	22	42379	34823729	c/t
rs2105915	22	42802	34824152	c/t
rs132648	22	42865	34824215	t/c
rs132649	22	43644	34824994	a/g
rs132650	22	45051	34826401	c/t
rs132651	22	45828	34827178	a/c
rs132652	22	45829	34827179	a/t
rs80584	22	46257	34827607	c/t
rs132653	22	47286	34828636	a/c
rs916334	22	47427	34828777	c/t
rs132654	22	47963	34829313	c/t
rs132655	22	48013	34829363	c/t
rs132656	22	48229	34829579	c/t
rs3834684	22	48282	34829632	-/a
rs132657	22	48376	34829726	-/g
rs916335	22	48404	34829754	a/g
rs132659	22	49900	34831250	c/t
rs132660	22	52699	34834049	g/t
rs132661	22	52897	34834247	a/g
rs132662	22	53414	34834764	a/g
rs132663	22	53487	34834837	a/t
rs132664	22	54112	34835462	g/t
rs132667	22	55492	34836842	a/g
rs132670	22	59766	34841116	c/t
rs132671	22	60307	34841657	a/g
rs132672	22	60701	34842051	a/g

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 13	Chromosome Position	Allele Variants
rs132673	22	60952	34842302	a/g
rs132674	22	61401	34842751	c/t
rs132675	22	62379	34843729	c/t
rs80585	22	62870	34844220	c/t
rs80586	22	62879	34844229	a/g
rs132676	22	63499	34844849	a/t
rs132677	22	64284	34845634	-/a
rs132678	22	64408	34845758	a/g
rs132680	22	64760	34846110	a/g
rs132681	22	65230	34846580	a/g
rs132683	22	66127	34847477	a/g
rs2269594	22	66634	34847984	c/t
rs132684	22	66686	34848036	a/g
rs132685	22	66694	34848044	c/g
rs132686	22	67113	34848463	a/g
rs132687	22	67257	34848607	a/g
rs132688	22	67403	34848753	a/g
rs132689	22	67609	34848959	a/g
rs132690	22	68418	34849768	-/a
rs132691	22	68610	34849960	c/g
rs132692	22	69629	34850979	c/t
rs132693	22	70024	34851374	a/g
rs132694	22	70848	34852198	a/g
rs132695	22	71428	34852778	c/g
rs1966266	22	71553	34852903	c/t
rs1966267	22	71633	34852983	a/g
rs106808	22	71768	34853118	a/c
rs132696	22	71769	34853119	a/g
rs2239829	22	73039	34854389	a/g
rs2285154	22	73325	34854675	a/g
rs2239830	22	73412	34854762	a/c
rs2239831	22	73547	34854897	c/t
rs3865722	22	73769	34855119	a/t
rs3865723	22	73806	34855156	a/g
rs3985996	22	74467	34855817	c/t
rs3985997	22	74472	34855822	c/t
rs3985998	22	74473	34855823	a/g
rs3985999	22	74482	34855832	c/t
rs3986000	22	74494	34855844	a/c
rs2413382	22	74592	34855942	a/g
rs2413383	22	74670	34856020	g/t
rs2413384	22	74672	34856022	g/t
rs2413385	22	74714	34856064	g/t
rs2413386	22	74723	34856073	a/t
rs1894606	22	74749	34856099	a/g
rs916336	22	74861	34856211	c/g
rs916337	22	74892	34856242	c/t
rs916338	22	74893	34856243	c/t
rs132697	22	75176	34856526	a/g
rs12781	22	75705	34857055	a/g
rs1053983	22	75989	34857339	a/g
rs1053982	22	76027	34857377	a/g

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 13	Chromosome Position	Allele Variants
rs2227167	22	77949	34859299	a/g
rs2227168	22	77974	34859324	c/t
rs132700	22	78167	34859517	c/t
rs3075364	22	78310	34859660	-/ct
rs2227169	22	78415	34859765	c/t
rs2097466	22	78575	34859925	c/t
rs2097467	22	78590	34859940	c/t
rs2413387	22	78709	34860059	c/t
rs132701	22	78875	34860225	c/t
rs132702	22	79864	34861214	c/t
rs132703	22	81316	34862666	c/t
rs2269595	22	81320	34862670	a/g
rs2269596	22	81409	34862759	c/t
rs132704	22	81737	34863087	c/t
rs2007468	22	81843	34863193	a/g
rs132705	22	82102	34863452	c/t
rs2007706	22	82833	34864183	c/t
rs132706	22	83461	34864811	c/t
rs132707	22	83624	34864974	c/t
rs132708	22	83660	34865010	c/g
rs132709	22	83701	34865051	a/t
rs132710	22	83708	34865058	a/g
rs132711	22	83782	34865132	c/t
rs132712	22	85707	34867057	a/g
rs132713	22	85717	34867067	a/g
rs132714	22	86486	34867836	c/t
rs132716	22	86833	34868183	a/g
rs132717	22	87115	34868465	c/t
rs132718	22	87234	34868584	a/g
rs132719	22	87479	34868829	g/t
rs132720	22	87561	34868911	a/g
rs132721	22	87604	34868954	a/g
rs132722	22	87674	34869024	c/t
rs132723	22	87958	34869308	a/g
rs132724	22	87992	34869342	-/g
rs132725	22	88019	34869369	a/g
rs132726	22	88074	34869424	c/g
rs132727	22	88079	34869429	c/g
rs132728	22	88115	34869465	a/g
rs132729	22	88118	34869468	c/g
rs132730	22	88120	34869470	a/g
rs132731	22	88135	34869485	-/ctcat
rs132732	22	88142	34869492	g/t
rs132733	22	88143	34869493	g/t
rs140575	22	88149	34869499	aca/tg
rs132734	22	88340	34869690	a/g
rs132735	22	88344	34869694	g/t
rs80587	22	88512	34869862	c/g
rs132736	22	88521	34869871	c/t
rs132737	22	88650	34870000	c/g
rs132738	22	88827	34870177	c/t
rs1807673	22	89230	34870580	a/g

dbSNP rs#	Chromo- some	Position in SEQ ID NO: 13	Chromosome Position	Allele Variants
rs2014700	22	89236	34870586	a/g
rs132739	22	90754	34872104	g/a
rs1812023	22	90984	34872334	a/g
rs1812024	22	91110	34872460	a/g
rs2005590	22	92026	34873376	c/t
rs132740	22	92954	34874304	c/t
rs3986001	22	93375	34874725	-/ttgc
rs2413390	22	93794	34875144	c/t
rs132743	22	94937	34876287	c/g
rs132744	22	95068	34876418	c/t
rs2413391	22	96188	34877538	a/g
rs132749	22	97092	34878442	c/t
rs132750	22	98812	34880162	c/t
rs132741	22	not mapped	not mapped	a/c
rs2413388	22	not mapped	not mapped	a/t
rs2413389	22	not mapped	not mapped	c/g

Assay for Verifying and Allelotyping SNPs

[0323] The methods used to verify and allelotype the 219 proximal SNPs of Table 60 are the same methods described in Examples 1 and 2 herein. The primers and probes used in these assays are provided in Table 61 and Table 62, respectively.

TABLE 61

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs3888818	ACGTTGGATGTGAGGTCAGGAGTTTGAGAC	ACGTTGGATGCCATGCCAGCTAATTTTCG
rs2010605	ACGTTGGATGTGTGCTTTTATGTCTTAGG	ACGTTGGATGGACTTTTAGAAGAAAAGTAC
rs743919	ACGTTGGATGTTCTTCACCAAGCCCTCTTC	ACGTTGGATGCCCAACACACACAAAGATGG
rs1008134	ACGTTGGATGACATATCCGGGCATCTTTTC	ACGTTGGATGCATCCACAGGATGCAATATC
rs132607	ACGTTGGATGTAGTTTGACGGTCACAAGGG	ACGTTGGATGGGAAGGAAGACCCAAACAGC
rs1476029	ACGTTGGATGTGGGTGACAGAGATCCTTAC	ACGTTGGATGAAACTCAGGGAAACGGACTC
rs1476030	ACGTTGGATGATCCTAGCACTGGGATTG	ACGTTGGATGCGTTTCCCTGAGTTTCACTG
rs2413380	ACGTTGGATGATGATACTGAGTCCAGGAGG	ACGTTGGATGAAAGGCTACTTCTTGCTCAC
rs2051609	ACGTTGGATGTAATCCCAGCACTTTGGGAG	ACGTTGGATGACAGACGGGGTTTCATCATG
rs2413381	ACGTTGGATGAGGGCTGCAGTAGAAAAGCG	ACGTTGGATGACGATGCGTGTGCCGACAG
rs1894604	ACGTTGGATGAAGTGCTGCTGCAAAAAGAG	ACGTTGGATGTTCTCCACTTCCATTCTGTG
rs1894605	ACGTTGGATGTGATGAGAGATGCAGATCGC	ACGTTGGATGTATTCAGAATTCAGCCTGCG
rs132609	ACGTTGGATGGCATTGAAAGGTCCGTATC	ACGTTGGATGCCCAAATCTGTCTTTTAGCC
rs132610	ACGTTGGATGTTCTACAAGAGCTAGGGACC	ACGTTGGATGGATCTATTGCTGCTTAGGCC
rs132611	ACGTTGGATGGCCTTCTTTACTCTGTCTC	ACGTTGGATGGGTTTTCTTTCAGGTCCTCC
rs132612	ACGTTGGATGAAAAATCTTCCCGCTACCTC	ACGTTGGATGTTCTGTGAGCTTCTCTCTG
rs1008790	ACGTTGGATGGTGAGGTCCCTTTTATGATG	ACGTTGGATGATAACAGCCCTGACAGATG
rs23085	ACGTTGGATGAAACCGTGCCAGCTGAGGAT	ACGTTGGATGGTCGGCAAGGAAGAGGAATC
rs105161	ACGTTGGATGAAGGAGCGGGAAATCTTTTG	ACGTTGGATGGTAGGAGGCTGAAATGCTAG
rs132613	ACGTTGGATGATGTAAAACCAATGGCCTCC	ACGTTGGATGAAGCTTCAGATTGTTACCC
rs132614	ACGTTGGATGCAAGAGCCCTGCTTTGTGAG	ACGTTGGATGTCCTGCACCAGCAGAGATGA
rs132615	ACGTTGGATGAAATCTGGAGGCTTGGTGAC	ACGTTGGATGTGAGCATTACATGGGACAG
rs132617	ACGTTGGATGGAGAAGAAGAGTGTGTGTGC	ACGTTGGATGACAGCCACCTGAATTTGTGC
rs3865724	ACGTTGGATGTTCTGGATAATTCCCATTC	ACGTTGGATGGCTGGATCACTGAAGAAGTA

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs2019657	ACGTTGGATGACGCCAGAACATTGTGTTTC	ACGTTGGATGGTGCCAGAAACATTCAAAGC
rs3865725	ACGTTGGATGAATATAGAACTGCTGGGCGC	ACGTTGGATGTGACTTAGGAGAGGTTCTGG
rs2019364	ACGTTGGATGTGACTTAGGAGAGGTTCTGG	ACGTTGGATGAATATAGAACTGCTGGGCGC
rs2008383	ACGTTGGATGTGATTCTAGGAGCAGGACTG	ACGTTGGATGACATGGGTGACCCTATCAAG
rs3986002	ACGTTGGATGCTTCTGTCTTCTCTGTGTC	ACGTTGGATGCAGGCAGAGGATTTGTTTGG
rs3888942	ACGTTGGATGCTGGGCTTTTGTGCTAAGAG	ACGTTGGATGGGGCCAATTTGCCCATAAA
rs3888943	ACGTTGGATGCTGGGCTTTTGTGCTAAGAG	ACGTTGGATGTTGGGCCAATTTGCCCATATA
rs3888944	ACGTTGGATGATACAGCCCTTGCCACTATG	ACGTTGGATGTTGAAGACATGGAAGCAGGG
rs132618	ACGTTGGATGAATCCGTGCCATCAGGCAAG	ACGTTGGATGCCTGCAATCGTTCTCTCTGC
rs132619	ACGTTGGATGTCATCAGCAGAAGCTGAAGC	ACGTTGGATGGGTGTGATGTCACGCATAAC
rs3827346	ACGTTGGATGAAGAGGTCCACAGAGGCTG	ACGTTGGATGAAAACAAGACCAGCAAGGGA
rs132620	ACGTTGGATGTCACATTAGATCAGGAAGCC	ACGTTGGATGTTAGGCCAGTTTAGCAGAAA
rs132621	ACGTTGGATGCTTCAAATCTGCAACTGGTG	ACGTTGGATGGATAGCTTAAGGACTCAGAG
rs80575	ACGTTGGATGGCTGCACATGAACTCTCAAG	ACGTTGGATGTGACATGTGACAGTGAGACC
rs80576	ACGTTGGATGTGAAGCTGTCACCTGCTAAG	ACGTTGGATGAACTCTCAAGCCACTTGACG
rs80577	ACGTTGGATGAGTCCATAAGAGGTTCCATG	ACGTTGGATGAACTAATGCCTTAGCAGGTG
rs80578	ACGTTGGATGACTGTTTCCCTGACAGCATG	ACGTTGGATGTGTAGAACAGAAGAGGGTCC
rs80579	ACGTTGGATGTGGGAGTAGGGTGAGAAGAG	ACGTTGGATGACTCACTGGTCTCTGCAAG
rs80580	ACGTTGGATGTTCAATCAGATGGGCGTGTG	ACGTTGGATGGATGGCATCATGCTACTTGG
rs132622	ACGTTGGATGTATGTCTTGGAGACTGGGAC	ACGTTGGATGACCTGCTGTTCAATTCTCAGG
rs132623	ACGTTGGATGAGCTCTGTCCAATCCATTG	ACGTTGGATGCTGAGGAAGTGCACAAACAC
rs132624	ACGTTGGATGTGCTGGGATTACAGGCATGA	ACGTTGGATGTCAAAGAAAGTCTCTGCTGGG
rs132625	ACGTTGGATGTTTCACGCCATTCTCCTGCC	ACGTTGGATGCGATGAAACCCCGTCTGTAC
rs132626	ACGTTGGATGTGGAGTGCAGTGGCATGATC	ACGTTGGATGGCAGGAGAATGGCGTGAAAC
rs132627	ACGTTGGATGAGGAGAATGGCGTGAAACCG	ACGTTGGATGAGACAGAGTCTTGCTTGTC
rs1807672	ACGTTGGATGGTGTGCTACAGCCTAAATGG	ACGTTGGATGAATACCCCATGTGACAGCTG
rs132628	ACGTTGGATGTATAGACTGAGTTGTGTGCC	ACGTTGGATGTCTTAAAGGCTCAATCTCC
rs132629	ACGTTGGATGCTCTCTCCCTGTCTCTCTTT	ACGTTGGATGTGTGTCTCTCATGGCCTTC
rs132630	ACGTTGGATGTTCCAAGGTGAAGGTGCCAG	ACGTTGGATGAAGGCCATGTGAGGACACAG
rs132631	ACGTTGGATGGGTGGCTCCAACAAGTATG	ACGTTGGATGATCAACCCTGCTGGCACCTT
rs132632	ACGTTGGATGCTTGAATTTTGCCTCCAG	ACGTTGGATGTCAGGATGCCTTAGTAAAC
rs132633	ACGTTGGATGAGAAGAGTGATTACCAGGG	ACGTTGGATGGGAAAGCTCACTTTCTGGTG
rs132634	ACGTTGGATGAAGTGCCATGGTGTCTTGTG	ACGTTGGATGGAAAGCATGGTGGAAAGCTC
rs132635	ACGTTGGATGAATAGGCACATGGCAGAAGG	ACGTTGGATGCACCAGAAAGTGAGCTTTCC
rs132636	ACGTTGGATGAAGCGTTTGACAATAGGCAC	ACGTTGGATGAAAGTGAGCTTTCCACCATG
rs129603	ACGTTGGATGGTGTGATATTGACACAGATTG	ACGTTGGATGAGGGTGTATATATATATACCC
rs132637	ACGTTGGATGGCATCTTAGTACACAGCAGG	ACGTTGGATGTTCCCAAATCCCTGCAAAAC
rs3788518	ACGTTGGATGAATCCTTCAGAAGGGCTTGG	ACGTTGGATGGCCGCGTTATTAAACCACAG
rs132638	ACGTTGGATGCATCCTTTCAGTGAAGGAGG	ACGTTGGATGTTGCCAAGGCAACTCAGTGA
rs132639	ACGTTGGATGACACCTGGGCAAACAAAAGC	ACGTTGGATGAAGTTCCCATAGTTGGCAG
rs132640	ACGTTGGATGTAAGAAGCTCCAGGTGACAC	ACGTTGGATGAAAAGAGTGACTCAGCGTCC
rs132641	ACGTTGGATGAGGGTCAGCTGGGAGCAGA	ACGTTGGATGAGGGCTGAGAGAGGAGGTTG
rs132642	ACGTTGGATGAAGAAGCAAGCCTACCTGAG	ACGTTGGATGAAACGAACCCTTCCAGTCAG
rs132643	ACGTTGGATGATCACAGACACCCAGTACAC	ACGTTGGATGACGTTCTGACAATGACCTGG
rs132644	ACGTTGGATGGCATAGAGTGCAAGACACAG	ACGTTGGATGGGGCTCCACTCCCTTAAATA
rs132645	ACGTTGGATGTGAAGGCAAACAGTACAAGA	ACGTTGGATGAAGTTAACCAAGTGTTTAC
rs2017329	ACGTTGGATGCCTTCCCAATTAAGAGCAGC	ACGTTGGATGGGGCAACAAGAGTGAAATTC
rs739198	ACGTTGGATGAAACTTTGGTCTCCACAACC	ACGTTGGATGTGAGTTTGTCTAAAGACCGG
rs132647	ACGTTGGATGCCTCACTACAGAAACCATGG	ACGTTGGATGAACTCAACTGGTTCAACCAC
rs2097465	ACGTTGGATGGAATTGACCAAACTGCAGGC	ACGTTGGATGAGGGTTGAAGCTGGATACTG
rs2105915	ACGTTGGATGAACCCAGGAGTTTCAGGACAA	ACGTTGGATGGGGAACTACAAGTGCATCAC
rs132648	ACGTTGGATGGTGGCTCAGGGCTGTAATTC	ACGTTGGATGTGTCCTGAACTCCTGGGTTT

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs132649	ACGTTGGATGGTCCTCCCCAGTCTTATTAC	ACGTTGGATGATTGAGAGGTTAGCTGGCTC
rs132650	ACGTTGGATGAAAGTGCTGGGATTACAGGC	ACGTTGGATGCTAAATCTCCTGCCATAGGG
rs132651	ACGTTGGATGAGGTCAGGTGTTGACCTTCC	ACGTTGGATGAGCAGGGTAGGGCATCCTAA
rs132652	ACGTTGGATGAGCAGGGTAGGGCATCCTAAC	ACGTTGGATGAGGTCAGGTGTTGACCTTCC
rs80584	ACGTTGGATGCATGGAGTCCTGTGATCTAC	ACGTTGGATGAAACTGAGGCCATGGGAGAT
rs132653	ACGTTGGATGCAGCCGTGCATCTGCATAAT	ACGTTGGATGCACTTTCCCTTTTGGGTTCC
rs916334	ACGTTGGATGAAACAGGATGCTTCCCAGCC	ACGTTGGATGCTGCTCTTGGATCAGCAGGA
rs132654	ACGTTGGATGTAAGGAAGTGTCAGAAAGCC	ACGTTGGATGAAATGATCCTCCTGCCTCAG
rs132655	ACGTTGGATGACTTTTCCAGGTGAAGGTAG	ACGTTGGATGTTGTGAACGCCATACCTGT
rs132656	ACGTTGGATGTCAGTAGAAGCAAGGAACCC	ACGTTGGATGCCAGGTTGACTGAACAAAG
rs3834684	ACGTTGGATGAGCCCTTGTTCACTAGAAGC	ACGTTGGATGGGTGGATGTGGGAGTAAAAG
rs132657	ACGTTGGATGGGCTGACTGACAATTACCTG	ACGTTGGATGAGGGCTCTGAGCTTTTCAAG
rs916335	ACGTTGGATGGATGACGAGAAAAAGGTGGG	ACGTTGGATGATTGAAGGATGCAGTCTTG
rs132659	ACGTTGGATGGGCCCATAGTGGGTCTAAC	ACGTTGGATGGTGGGGTGAGTGCCCAAAAG
rs132660	ACGTTGGATGTACATGTGGTTGTACCCTCC	ACGTTGGATGCTGGCATGGTTTTACCCATC
rs132661	ACGTTGGATGCTTCGAGAAATCATTCCGC	ACGTTGGATGCCAAAATGCAAGCTCAAGGC
rs132662	ACGTTGGATGCATCTCTTAAATGGGCCAGG	ACGTTGGATGTTGAAAGCCACAGCCTCATG
rs132663	ACGTTGGATGCCACTAACGGATTGAGATC	ACGTTGGATGTGGCTTTCAACCAGCAACTC
rs132664	ACGTTGGATGATCATGCCACTGCAATCCAG	ACGTTGGATGGCATATGTGACTGCTTCCTC
rs132667	ACGTTGGATGCTGGAGAAATCAAATAGAGAG	ACGTTGGATGTGTACAGCTTTTGACAGTTG
rs132670	ACGTTGGATGTAAGGTCGGGAGTTCAAGAC	ACGTTGGATGACGCCCGGCTGATTTTGTAT
rs132671	ACGTTGGATGGTGAGCCATACCATCACATC	ACGTTGGATGCTGTAGTAAAGGTCTGGTCG
rs132672	ACGTTGGATGCTCCCCAATAAGCTCAACAC	ACGTTGGATGCTGTTAGGGCAATGAAAGGC
rs132673	ACGTTGGATGTGAGTAGTTGGTGTGAGTGG	ACGTTGGATGCAATGGATGAAGCTGATCCC
rs132674	ACGTTGGATGAACTGTAGTCCCAGCTACTC	ACGTTGGATGTAGCTCTATCACTCATGCTG
rs132675	ACGTTGGATGGTAGAGCAGATGTGCAATGG	ACGTTGGATGTCCTAACCATCTGCCTTGTG
rs80585	ACGTTGGATGCTGTTGTTCCAACACTTCAC	ACGTTGGATGGGTCTGCTACTAGAATTACAG
rs80586	ACGTTGGATGGTAAGTGTAAGAAGGTCTGC	ACGTTGGATGCAAGGCATAATATTCTGACC
rs132676	ACGTTGGATGCAAACATTCTGCAGAAAGCG	ACGTTGGATGAAGCGTGTGCTGAGAAATG
rs132677	ACGTTGGATGCTCTGTTACAAAATGAAGGG	ACGTTGGATGGCTATCTAGGCTAAAAATCCC
rs132678	ACGTTGGATGAAGGCACTGAAAATGCCTAG	ACGTTGGATGGGAATCCAGATGCTTACATG
rs132680	ACGTTGGATGGCCTTAGCTATCATGTTCTC	ACGTTGGATGGCGTGTGTTAAGGCAATTCTC
rs132681	ACGTTGGATGTACTGAAGCCTGAGACTAGC	ACGTTGGATGCTAGCAGAACTAACCGAGC
rs132683	ACGTTGGATGTTACCCTATGGTAATGGCAG	ACGTTGGATGACTGATTAGTACAGGAAGGG
rs2269594	ACGTTGGATGTGGCATGGCTAAAAGGACAG	ACGTTGGATGGATTGTTCTGATGCCAGTG
rs132684	ACGTTGGATGCCTTTTAGCCATGCCATTCTG	ACGTTGGATGTCAGTGTAACACGTGCCACC
rs132685	ACGTTGGATGTCAGTGTAACACGTGCCACC	ACGTTGGATGCCTTTTAGCCATGCCATTCTG
rs132686	ACGTTGGATGCAGAATATCCACGTCAGGTG	ACGTTGGATGGACAGCTTAGGACTATGTGC
rs132687	ACGTTGGATGCAACTGTAAGCAGCCCATTG	ACGTTGGATGCTGACGGTGCAAATGGATAC
rs132688	ACGTTGGATGAGTACTACAGGACGTGCTTG	ACGTTGGATGGGTGCGCTCATATATGGTAG
rs132689	ACGTTGGATGTACTGGGACAGTCTGCTTTC	ACGTTGGATGACTTTACAGTGCTGGAGCAG
rs132690	ACGTTGGATGTGTTTTGCTTTGCGCTCTCC	ACGTTGGATGTCTGCAACCAACTCTTTGGG
rs132691	ACGTTGGATGGTCAAAGCCAGGCATTTGTC	ACGTTGGATGCTGTCTATCTTGTGGAAAGGG
rs132692	ACGTTGGATGGAATCTAAGCCAGCTGTTGG	ACGTTGGATGGGAGCATCATGTGGATTCTT
rs132693	ACGTTGGATGGCCAGAAGAAAAGAGTGTGG	ACGTTGGATGATTCTGCATGTGGAACGTCC
rs132694	ACGTTGGATGATAGAGACTGAGAGCTGCAG	ACGTTGGATGCAGAACAAAGCAGGAAGCTC
rs132695	ACGTTGGATGGCCTCTCTATGACTACAC	ACGTTGGATGTTACAGCAGGGAACCTTTC
rs1966266	ACGTTGGATGTGATTGTACAAGGCAGACCC	ACGTTGGATGTGTAAGCACCTGCATTACAGC
rs1966267	ACGTTGGATGTAATCACAGACCATGAGGG	ACGTTGGATGGGAGGAAAGCACAGCAGAAT
rs106808	ACGTTGGATGAACAAGGCAGATCCTTCCCG	ACGTTGGATGATGGTTCTTGAAGAGCAGTG
rs132696	ACGTTGGATGATGGTTCTTGAAGAGCAGTG	ACGTTGGATGAACAAGGCAGATCCTTCCCG
rs2239829	ACGTTGGATGTGCTTTGTCTCGTTCGGATGG	ACGTTGGATGAAAGAGCGAAACTCCGTCTC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs2285154	ACGTTGGATGTGAACTCAAATGATCCGCCC	ACGTTGGATGAAGAACCCTTTTCGACTGGG
rs2239830	ACGTTGGATGAAACCCTAATGGGAAGCCTC	ACGTTGGATGTGTGGTAGCAAGCAGTTGAC
rs2239831	ACGTTGGATGAGAACAGTCACTGACCCAAG	ACGTTGGATGGCTCCACACACTTTGATTCC
rs3865722	ACGTTGGATGCCACTGTACTGCTAGTATTG	ACGTTGGATGACCTGCTCTAGTTTTCATCC
rs3865723	ACGTTGGATGCCTGCATTTGATGCAATTCC	ACGTTGGATGGTTTCTGTTTCTGTTGCTTGC
rs3985996	ACGTTGGATGACATGGGTGACCCTATCAAG	ACGTTGGATGTGATTCTAGGAGCAGGACTG
rs3985997	ACGTTGGATGCAAGAATTTCTCCCGGCATC	ACGTTGGATGTGATTCTAGGAGCAGGACTG
rs3985998	ACGTTGGATGTGATTCTAGGAGCAGGACTG	ACGTTGGATGCAAGAATTTCTCCCGGCATC
rs3985999	ACGTTGGATGTGATTCTAGGAGCAGGACTG	ACGTTGGATGCAAGAATTTCTCCCGGCATC
rs3986000	ACGTTGGATGCAGGCAGAGGATTTGTTTGG	ACGTTGGATGCTTCTGTCTTCTCTGTGTC
rs2413382	ACGTTGGATGAAACAAATCCTCTGCCTGGG	ACGTTGGATGAAAAGCCCAGAGCCTTCATG
rs2413383	ACGTTGGATGCTGGGCTTTTGTGCTAAGAG	ACGTTGGATGGGGCCAAGTTGACCCATAAA
rs2413384	ACGTTGGATGCTGGGCTTTTGTGCTAAGAG	ACGTTGGATGGGGCCAAGTTGACCCATAAA
rs2413385	ACGTTGGATGAATGGTCTTCGCTGATACAC	ACGTTGGATGATGGAAGCCGGTGTGTTGATG
rs2413386	ACGTTGGATGTTTTATGGGTCAACTTGGCC	ACGTTGGATGTTCCAAAATGGTCTTCGCTG
rs1894606	ACGTTGGATGTTTTATGGGTCAACTTGGCC	ACGTTGGATGAGACTCCTGCAAAGCTTCC
rs916336	ACGTTGGATGGGATGAGGGTATTTGCTGTC	ACGTTGGATGGGCCTGTATGTAGGTTGAAG
rs916337	ACGTTGGATGAGATCAGAAGGGCCTGTATG	ACGTTGGATGATTTGCTGTCTGGCTGTCTC
rs916338	ACGTTGGATGATTTGCTGTCTGGCTGTCTC	ACGTTGGATGAGATCAGAAGGGCCTGTATG
rs132697	ACGTTGGATGCATGAGGAAGAGAAGTCAGG	ACGTTGGATGACACTGACTGATGACTGAGC
rs12781	ACGTTGGATGTTACACACAGGGCACTCAGC	ACGTTGGATGGAGCCAGAAAATTAAGTAAAA GC
rs1053983	ACGTTGGATGCCATCATCAAGAAGCCACTG	ACGTTGGATGTGTCTTACCAGCATCCACTC
rs1053982	ACGTTGGATGGGAGAGTGGATGCTGGTAAG	ACGTTGGATGCGGTTGAATGTCTTCCAAG
rs2227167	ACGTTGGATGCTCCTGAGTGTATGGACATC	ACGTTGGATGGGCATTAAGGGACATTCTGC
rs2227168	ACGTTGGATGCCAATTGGAGGCATTAAGGG	ACGTTGGATGCTCCTGAGTGTATGGACATC
rs132700	ACGTTGGATGAATGTGGTGTCTGGCTCCAC	ACGTTGGATGCTCAGCCCTGCTGTAAATGG
rs3075364	ACGTTGGATGGAACAGCAGTTTAGGGAGTG	ACGTTGGATGCGAAGCCTTTCTATGGACTC
rs2227169	ACGTTGGATGAGGTAAGTAAGCTGCCTTTC	ACGTTGGATGTTTCAAGGCTTCATAGAGAGC
rs2097466	ACGTTGGATGCTGGGATTACAAGCATGAGC	ACGTTGGATGCTGCATAAATCACAGAGCTG
rs2097467	ACGTTGGATGATCTCCTGACCTTGTGATCC	ACGTTGGATGATTCTTTTCAAGGCCGGGCG
rs2413387	ACGTTGGATGAAGTAGCTGGGACTACAGGC	ACGTTGGATGTAACACGGTGAACCCCGTC
rs132701	ACGTTGGATGGTGGCATATCTATGTTGTAC	ACGTTGGATGGCGAGACTCCATCTCAAAAA
rs132702	ACGTTGGATGGAAGCTCACCCAGTTAAGGA	ACGTTGGATGCCCCTGTAACAACAATCCTG
rs132703	ACGTTGGATGCTTGACCTGATCAATGTGTG	ACGTTGGATGTTTGTGCAAGTTCCTCAGAAG
rs2269595	ACGTTGGATGAGAAGTTTCAAGAAAAGGGCC	ACGTTGGATGCAGCAGGACTTTCTTTGGGA
rs2269596	ACGTTGGATGAGGTGCTCAGTTAGCGTTAC	ACGTTGGATGTCCCAAAGAAAGTCTGCTG
rs132704	ACGTTGGATGATATTCTTCTGCACTGCTG	ACGTTGGATGATCTCCCCGGGCTAGTTTTTC
rs2007468	ACGTTGGATGAGGTTACCTGGGCAATTACAG	ACGTTGGATGGAAAATCCTGCTGACTAGCG
rs132705	ACGTTGGATGTTTTGATGGAGGCACCAAGTG	ACGTTGGATGTCTCCAAATACGGTCACTGG
rs2007706	ACGTTGGATGCCAGGAATTTACATAAGGG	ACGTTGGATGTTGAACATAGCAAGAGTGAG
rs132706	ACGTTGGATGAAGGATCAGTGCTGAGGGTC	ACGTTGGATGATTCCTCCTGCTGGTCATGG
rs132707	ACGTTGGATGAATCCTTAGGAAGGGCTGGG	ACGTTGGATGAGCTGGCCCCGTTAGTAAAC
rs132708	ACGTTGGATGTCTTGTTCAGAGGGAGAGC	ACGTTGGATGTCTCAGCCAATCCCAGAATC
rs132709	ACGTTGGATGTGAGTCCTGTCCAAGATGAG	ACGTTGGATGAGCCCTTCTTAAGGATTCTG
rs132710	ACGTTGGATGTGAGTCCTGTCCAAGATGAG	ACGTTGGATGCCTAAGGATTCTGGGATTGG
rs132711	ACGTTGGATGTCATCTTGGACAGGACTCAG	ACGTTGGATGTTGCCATGGCAACCAAGTCA
rs132712	ACGTTGGATGGTCTTCAAGGCTGAGTGAGC	ACGTTGGATGACTCCACGTGGCCTCTCTTG
rs132713	ACGTTGGATGAAGGCTGAGTGAGCCCCAAC	ACGTTGGATGACTCCACGTGGCCTCTCTT
rs132714	ACGTTGGATGACACGGTGAAACCCCTTCTC	ACGTTGGATGAGTAGCTGGGACTACAGGTG
rs132716	ACGTTGGATGTGGATTTGCAATGAGGAGTC	ACGTTGGATGTCAATGACTGTGCTCTACTC
rs132717	ACGTTGGATGAATGTGGGCAGTTTTACGTG	ACGTTGGATGGATGGACCTTAGGGTGTTC

dbSNP rs#	Forward PCR primer	Reverse PCR primer
rs132718	ACGTTGGATGTCAGAGGGTATCAACATCTC	ACGTTGGATGTGGGCATCTTCATATACTGC
rs132719	ACGTTGGATGATACCCTCAGTTGTACCCAG	ACGTTGGATGCTGAACAAAGGAGAAGGAGG
rs132720	ACGTTGGATGATACTGGGTACAACTGAGGG	ACGTTGGATGCCTCTCCACCTTTTCCTAAC
rs132721	ACGTTGGATGCAGCTACAAAGTTGCTAATGG	ACGTTGGATGTCTTATTGTACCCTCCCTC
rs132722	ACGTTGGATGACAATGGTAATGCTTGGAGC	ACGTTGGATGGGGAGGGTACAAATAAGATG
rs132723	ACGTTGGATGACACAGATGTCTGTCTTCTG	ACGTTGGATGATACTCCCCTGGTGAATGCT
rs132724	ACGTTGGATGCCCCATGCAACAAGGGTAAA	ACGTTGGATGTGTCCCTTACAGCAAGAAGC
rs132725	ACGTTGGATGCCCCATGCAACAAGGGTAAA	ACGTTGGATGTGTCCCTTACAGCAAGAAGC
rs132726	ACGTTGGATGGGGTCACACAGTGAACAAAG	ACGTTGGATGTTCTTGCTGTAAGGGACAGG
rs132727	ACGTTGGATGGGGTCACACAGTGAACAAAG	ACGTTGGATGTTCTTGCTGTAAGGGACAGG
rs132728	ACGTTGGATGAGTTCTACTGGCTCATGGTG	ACGTTGGATGTTTCGCCTTCTTCCTGCTTTG
rs132729	ACGTTGGATGAGTTCTACTGGCTCATGGTG	ACGTTGGATGTTTCGCCTTCTTCCTGCTTTG
rs132730	ACGTTGGATGTTTCGCCTTCTTCCTGCTTTG	ACGTTGGATGAGTTCTACTGGCTCATGGTG
rs132731	ACGTTGGATGTTTGTTCACTGTGTGACCCC	ACGTTGGATGTCTGGTCTCCCAAGTTCTA
rs132732	ACGTTGGATGGCCAAGGCAACCATCTCAAC	ACGTTGGATGTGCAGCTCATCACAAGCGTC
rs132733	ACGTTGGATGGCAACCATCTCAACACCATG	ACGTTGGATGTGCAGCTCATCACAAGCGTC
rs140575	ACGTTGGATGTGCAGCTCATCACAAGCGTC	ACGTTGGATGCCATCTCAACACCATGAGCC
rs132734	ACGTTGGATGGGATACTGACTGTTAGCCTC	ACGTTGGATGCGGAATTGACCAACTGGTAG
rs132735	ACGTTGGATGGGATACTGACTGTTAGCCTC	ACGTTGGATGCGGAATTGACCAACTGGTAG
rs80587	ACGTTGGATGTCTGAGCCAAGCTCACCAGA	ACGTTGGATGTTTTCTGCCCAAGGAGGAG
rs132736	ACGTTGGATGTTTTCTGCCCAAGGAGGAG	ACGTTGGATGAAGCTCACCAGATGCAGACG
rs132737	ACGTTGGATGTCTAGGCAGCAATGAGCTAG	ACGTTGGATGTGCTCCTCCTGAGAAATCAC
rs132738	ACGTTGGATGTGAAGCCTGTAATCCCAGTG	ACGTTGGATGCATAGAGACAGCATCTCCTG
rs1807673	ACGTTGGATGTTGCAGTGAGCAGAGATTGC	ACGTTGGATGGTGAAATCTGAGTCGTGGTC
rs2014700	ACGTTGGATGTTGCAGTGAGCAGAGATTGC	ACGTTGGATGGTGAAATCTGAGTCGTGGTC
rs132739	ACGTTGGATGGGAATCAAAGAAGGTGGAGG	ACGTTGGATGTGGTTGTGGCCAGACCATAA
rs1812023	ACGTTGGATGAGCAGGAGGGAGGGAGCAAT	ACGTTGGATGGACCTCCCTCCATCTCCTTA
rs1812024	ACGTTGGATGTGTCAGAGGAAGATCCCTTG	ACGTTGGATGCCTCATAGAGCTATTGCGAG
rs2005590	ACGTTGGATGGGAGGCAATGCCTGATTTTG	ACGTTGGATGTGCTTCCACCACCTGGAAAA
rs132740	ACGTTGGATGTTTATTCTTCTTGTGCACAG	ACGTTGGATGCTTGACTGGTACCTAACAATG
rs3986001	ACGTTGGATGTTTTCTGACTTGGCATCACC	ACGTTGGATGCACAAAGTATTCCACCTTCC
rs2413390	ACGTTGGATGATAAATTCGTGGCTGAGCTC	ACGTTGGATGATCTTGTGGCATAAGGAGTC
rs132743	ACGTTGGATGACAGGGAGAAAAGTGAGGAAG	ACGTTGGATGCATCCTGTTTCCCCTAAAGG
rs132744	ACGTTGGATGGGGTCTGTTTCAGGAGCATG	ACGTTGGATGTCTATGGCTGATGGCCACAG
rs2413391	ACGTTGGATGGGGCAAAAGCAGAAATACTG	ACGTTGGATGCCCTCAAACCCTGTTTTCTG
rs132749	ACGTTGGATGCCATGCACTCTCTAGTACTC	ACGTTGGATGTGTGGCCTTGGGGAAATGAT
rs132750	ACGTTGGATGTCCTGTGCCTGTGGAACTC	ACGTTGGATGGGTTCTCCAGGTGGCAAAAG
rs132741	ACGTTGGATGCTACAATTTATCCGCACTAG	ACGTTGGATGGCCAAGTCAGAAAAATGAGAG
rs2413388	ACGTTGGATGTACAGAATTCAGACCAACCC	ACGTTGGATGGCCCTGAGATTTGATTTTCC
rs2413389	ACGTTGGATGGCTAGAATCTCATAACAGACG	ACGTTGGATGGCGTCCTACTATGATTTGTC

TABLE 62

dbSNP rs#	Extend Primer	Term Mix
rs3888818	TGAGACCAGCCTAGCCAAC	ACT
rs2010605	TGGTCCCAAGATATTCTATAGA	ACT
rs743919	CTCACCTAAGGACTGCCTCT	ACT
rs1008134	CCGGGCATCTTTTCTTCCATC	ACT
rs132607	GCAGGCAGGACAGCATGTG	ACT
rs1476029	CTTAGAGGCTATATTAAGACCA	ACG

dbSNP rs#	Extend Primer	Term Mix
rs1476030	TTTGGCAATACTGGCCTATTC	ACT
rs2413380	TCCAGGAGGGAAGACAACC	ACT
rs2051609	CGCTTGAGGTCAGGACCAG	CGT
rs2413381	GCGTGTTGCCAACAGCCTC	ACT
rs1894604	AAATGGGAGGGAATGTTGGC	ACG
rs1894605	TGCAGATCGCAACTGAGCG	ACT
rs132609	GTTTCTCAGAGGATCAGGGA	ACT
rs132610	GGTGTGAGATTTGGAGACTTT	ACG
rs132611	CTCTGTCCTCTAGCCCCC	ACT
rs132612	ATCTTCCCGCTACCTCAAGAGT	ACT
rs1008790	CATAATCACAAGTCCTATGATTA	ACT
rs23085	AGGATGACCATGGCAAGGAA	CGT
rs105161	GGCCCTGGCAGGAAACAG	ACG
rs132613	CCAATGGCCTCCACTGGC	ACT
rs132614	CGGCCACAGCGCTGCCC	ACG
rs132615	GCTTTCAGAACAACGGTAGAA	ACT
rs132617	AAGAGTGTGTGTGCAGTAGCAAG	ACG
rs3865724	TCACTTAAGCTTTGAATGTTTCTG	ACT
rs2019657	GCCAGAACATTGTGTTTCATTGT	ACG
rs3865725	GGCAAGAGATACAGAATGCACA	CGT
rs2019364	GTATCTCTTGCCCCTGCTC	ACG
rs2008383	GAAGGACAGAAGGCTGATGC	ACG
rs3986002	TCCTTCTCTGTGTCACTCCT	CGT
rs3888942	ACATGGAAGCAGGGGTTTGA	CGT
rs3888943	AGCAGGGGTTTGATGAAATCT	ACT
rs3888944	CATCCTCCACATTGGGCCAA	ACT
rs132618	AATCTCAGCTGGAAGTGG	CGT
rs132619	TGCAACCAGCATTGACCG	CGT
rs3827346	GAGGCTGCACCATCTCCAA	ACG
rs132620	GGAAGCCTTTATTCAGGATTGT	ACT
rs132621	TCAAATCTGCAACTGGTGTCAGAA	ACT
rs80575	GAAGCTCTCAAGCCACTTGAC	ACT
rs80576	GCTAAGGCATTAGTTTGGCTGG	ACG
rs80577	TGAAATTGCACATGGCATTGG	ACG
rs80578	ATGCCTGGGAACTGGGGC	ACT
rs80579	GGGAGGCACTGAGGGCATGAAA	ACT
rs80580	CTGAGAATGAACAGCAGGTCA	ACT
rs132622	ATAGTAGTTCAATCAGATGGGC	ACT
rs132623	ATTCCAGCCTCTCTGTGTTCTG	ACT
rs132624	ACAGGCATGAGCCGCTGC	ACT
rs132625	GGCCACCGCATCCGGCTA	CGT
rs132626	AGTGGCATGATCTCGGCCAC	ACG
rs132627	GAGGCGGAGGTTGCGGTG	ACT
rs1807672	CATTGAGAATAAGGTGGTTCTGA	ACT
rs132628	CCTCCAAATTCATATACTGAGACC	ACG
rs132629	TCTCTCTCTCTCACACAC	CGT
rs132630	CTGCTCCTGGCTTACAGAG	ACT
rs132631	TCACAGTTCTGGAGGCAAAAA	ACT
rs132632	TGGAATTTTTGCCTCCAGAACTGT	ACT

dbSNP rs#	Extend Primer	Term Mix
rs132633	AGTGATTACACAGGGAAGTGCCA	ACG
rs132634	GGTGCTTTGTGGAGGAACC	ACT
rs132635	ATTTCCCGTACATGGGGAGAAA	ACT
rs132636	TGACAATAGGCACATGGCAG	ACT
rs129603	GCTGCCATCCTAAACACATCTA	ACT
rs132637	ACACAGCAGGATTACTGCCCAGA	ACT
rs3788518	TGGGAGGCTCAAGGAAGAACTCT	ACT
rs132638	GGAAAAATAAAAGCAAAATACCC	ACT
rs132639	AAAGCAAACAGGCCTTCAGAA	CGT
rs132640	GGTGACACAGAGAAGACGTGGC	ACT
rs132641	GGGAGGTCAGAGGTCGGG	ACT
rs132642	GTCAGTGAAGAGACTTTCC	CGT
rs132643	GACACCCAGTACACACTGGCT	ACT
rs132644	TTTGGAATGAGGAGTCATTTACA	ACT
rs132645	CTCAACAGTAAGCAAGATTTAAA	ACT
rs2017329	TGATGTTTCAGATTTTCCTTTTTT	CGT
rs739198	TGGTCTCCACAACCTCTTATC	ACT
rs132647	AAACCATGGAAGTCTCTAGAGTCA	ACT
rs2097465	CAAACCTGCAGGCTTGCCAG	ACT
rs2105915	CAAGCCTGGGCAGCATAGCAC	ACT
rs132648	AATTCCTGCTAATGCACG	ACT
rs132649	CAGTCTTATTACTTTTGTACGAGG	ACT
rs132650	CATGAGCCACCGTGCCAG	ACT
rs132651	CCTCAGGGTTTTTCACCTGCCT	ACT
rs132652	AGGGCATCCTAACCCCTA	CGT
rs80584	ATCTACCTGCTCAACTTCCTGA	ACG
rs132653	AATAACCAGACACGTTCTCCAG	ACT
rs916334	GTCCAGCAGCACCCCTTGGT	ACG
rs132654	CGACAAGAGCAGGTCTGGAAC	ACT
rs132655	CAGAAGAACCCACATAAGGAA	ACT
rs132656	TCTTTGTCTTTTACTCCCACATCC	ACT
rs3834684	CACTAGAAGCAAGGAACCCCC	ACT
rs132657	TACCTGACAATCACCCCC	CGT
rs916335	TCAGGTAATTGTCAGTCAGCC	ACT
rs132659	AGAACTCCCCAAATCGTCCT	ACG
rs132660	CCCCAGAGTGGGCTTTTCT	ACT
rs132661	CCGCTCTCCCTCTGAGAGT	ACT
rs132662	TGATCTGAGTTTACAGGTGAG	ACT
rs132663	TGAGATCTGTCTCAGACGCA	CGT
rs132664	CTGGGCTAGAGAGGGAGAC	ACT
rs132667	CTTTAACTTTTGCTCACAAGAGT	ACT
rs132670	AGACCAGCCTGATCAACATG	ACT
rs132671	ACATCAATAGGCCTAAAAATCGTT	ACT
rs132672	GAAACTTGAAATTCCTTGAGAAAT	ACT
rs132673	GTGTGAGTGGGAAGCCTCC	ACG
rs132674	GGAGTTGGAGGCTGTAGTAA	ACT
rs132675	AGATGTGCAATGGAATTTGGCAA	ACT
rs80585	AGGCATAATATTCTGACCATTAAAG	ACG
rs80586	GGTCTGCTACTAGAATTCAGAA	ACG

dbSNP rs#	Extend Primer	Term Mix
rs132676	ATCCCTTAATATTGCATAGGAC	CGT
rs132677	GGGTTGAAGTACTATGCTAGT	CGT
rs132678	AGGTTAGTTCATGTAAGTCCAT	ACT
rs132680	TTTTATTTTAGCTTGAGCTTTTCA	ACG
rs132681	CTAGCTCTAAATCACATTCTGC	ACG
rs132683	CAGGCCCATACCCAAAATATGCT	ACT
rs2269594	TGGCTAAAAGGACAGATAGAG	ACT
rs132684	GACACTAAGAGCGGTGAGAC	ACT
rs132685	CGTGCCACCCAACTGGAGA	ACT
rs132686	TGTGCATCTTATGGTGTACCA	ACG
rs132687	TCGTTACCCCCATTCTATCC	ACT
rs132688	ACAGGACGTGCTTGAAAGAG	ACG
rs132689	TGGCGATGGCCTCTGCTC	ACT
rs132690	GCTCTCCTTGCTTCAAAAAAAAAA	CGT
rs132691	TGACCTATCCTGCTTCAGGT	ACT
rs132692	CGAAGTGTGTTAGCTCATGAC	ACT
rs132693	GAGTGTGGACACCAGGTCA	ACT
rs132694	CACCTTAGGAATGGCAGCTTC	ACG
rs132695	TATGACTACACATGCTGGCAAAC	ACT
rs1966266	GCAGACCCCTAACTCTAATTTG	ACG
rs1966267	CACTGAGTTATGAGTACTCAAC	ACT
rs106808	GATCCTTCCCGAGGACACC	ACT
rs132696	CAGGCTGCCTGGAAGGAGA	ACT
rs2239829	GATGGCTGGATTCATAACAGGTAA	ACT
rs2285154	AGTGCTGGGATTACAGGCAT	ACT
rs2239830	CAGTCACCTGAATTTGTGCTTATT	ACT
rs2239831	GTCAGTACCCAAAGCTATCCTC	ACG
rs3865722	CAATTGCAAGCAACAGAAACAGAA	CGT
rs3865723	TCCACTGTACTGCTAGTATTG	ACG
rs3985996	AGAATTTCTCCCGGCATCAG	ACG
rs3985997	TCTCCCGGCATCAGCCTTC	ACG
rs3985998	GGGAGGAGTGACACAGAGAAGGA	ACG
rs3985999	GGGGTACTGGGAGGAGTGACAC	ACT
rs3986000	GCAGGACTGGGGTACTGG	ACT
rs2413382	CAGGGGAAGTCAAGGCCACA	ACT
rs2413383	AGCCATTGAAGACATGGAAGCC	ACT
rs2413384	ATTGAAGACATGGAAGCCGG	ACT
rs2413385	GGCCAGCTCTTCCTCCAC	CGT
rs2413386	CTTGGCCCAATGTGGAGGA	CGT
rs1894606	CCTAGCGGCAAGGGCTGT	ACT
rs916336	AGGGTATTTGCTGTCTGGCTGTCT	ACT
rs916337	AAGGGCCTGTATGTAGGTTGAA	ACT
rs916338	CCCTCTATGTCTCATGGATTTTCC	ACG
rs132697	CCTAGGGGAGCCCATATATCA	ACT
rs12781	AGACAGCTCGAGAGATCC	ACT
rs1053983	GCTGACTCAGATACACCCC	ACG
rs1053982	GATGCTGGTAAGACAGGG	ACG
rs2227167	CGTCAAATCAAGTGCAA	ACT
rs2227168	CATTAAGGGACATTCTGC	ACT

dbSNP rs#	Extend Primer	Term Mix
rs132700	ATCCTGTCTGTCATTGGCGTT	ACT
rs3075364	GTTTAGGGAGTGGTTTTTGAAAG	CGT
rs2227169	TGTCCTTTATTGGTACAGGGAAGA	ACT
rs2097466	TACAAGCATGAGCCACCGC	ACT
rs2097467	TC CCAAAGTGCTGGGATTACA	ACT
rs2413387	TACAGGCACTCACCACCAC	ACT
rs132701	TGTACAAAACATATTTAACCTTGA	ACT
rs132702	CACCCAGTTAAGGAAAAATTCCT	ACT
rs132703	GATCAATGTGTGTTCCCGGA	ACT
rs2269595	GCCCCAGACAGCATCTCC	ACT
rs2269596	TTGCTGGCAAGAGACCAGG	ACT
rs132704	GGGCTGCCTGGAGGAGG	ACG
rs2007468	TGGGCAATTCAGCCACACGCAC	ACT
rs132705	TATAGACTGAATTGTGTGCC	ACG
rs2007706	GGAATTTACATAAGGGTCTATAG	ACT
rs132706	GAACCCCTCCACTGCCC	ACT
rs132707	GCTCTCCCTCTGAAACAAGATG	ACT
rs132708	GAGAGCTTCTTCCTTGCC	ACT
rs132709	CAGGGAAGATTAGAAGCTGAGAGC	CGT
rs132710	GGGCAGGGAAGATTAGAAGC	ACG
rs132711	TTTGCTGTCCAGGGCGGC	ACG
rs132712	AACCCAGACGGAGGTGGC	ACG
rs132713	GCCCCAACGGAACCCAGA	ACG
rs132714	CCCCTTCTCTACTGAAAATACAAA	ACT
rs132716	TGAGGAGTCATTTACCATGAG	ACG
rs132717	GCAGTTTTACGTGAAGGAGG	ACT
rs132718	GTTTTATACCTAGAGCCACACT	ACT
rs132719	TACCCAGTATTTCTTAACCTCC	CGT
rs132720	CAGCTACAAAGTTGCTAATGG	ACT
rs132721	ATGTTAGGAAAAGGTGGAGAG	ACT
rs132722	CCTAACTGGGATGGGCCTGAA	ACT
rs132723	TTCTGGGGCCCCCATGCA	ACT
rs132724	ACCCAGTCCTGGGCAGCA	ACT
rs132725	GGGAGTATGCAGAGGGGC	ACT
rs132726	CAGTGAACAAAGCAGGAAGAAGG	ACT
rs132727	GTCACACAGTGAACAAAGCAGGAA	ACT
rs132728	CATGGTGTGAGATGGTTGCC	ACG
rs132729	GCTCATGGTGTGAGATGGTT	ACT
rs132730	GTGACCCCTAGGCCAAGGCA	ACT
rs132731	GGCAACCATCTCAACACCAT	ACT
rs132732	AACCATCTCAACACCATGAGCCA	ACT
rs132733	ATCTCAACACCATGAGCCAG	ACT
rs140575	GCTCTCTCCTGGTCCTCC	ACG
rs132734	AGCCTCAACTAGGACACA	ACT
rs132735	TCAACTAGGACACAGTGC	ACT
rs80587	GCCAAGCTCACCAGATGCAGA	ACT
rs132736	AGGGAGCTGCTTTGCTGAAA	ACT
rs132737	CCTGCAGCCTGGGTGACA	ACT
rs132738	GGCAGGAGTTCAAGACAGCCTG	ACT

dbSNP rs#	Extend Primer	Term Mix
rs1807673	GGGCAACAGAGCGAGACTCC	ACT
rs2014700	GAGCGAGACTCCATCTCA	ACT
rs132739	GGGAGGTGACCTGGAGCC	ACG
rs1812023	GCAATCAGACTCAAGCCTGG	ACT
rs1812024	GGGATGGTGTGACCTCCC	ACG
rs2005590	CAATGCCTGATTTTGTCACTGAAC	ACT
rs132740	GGCATATGTGCATTTGTCTGAG	ACG
rs3986001	TCCTTTTTC TAAACCCCTGCAA	ACT
rs2413390	GGCTGAGCTCAAGGTTTTAAA	ACT
rs132743	GGAGAAAGT GAGGAAGAAAATTA	ACT
rs132744	TGGGGTTACAGTTGGTCATAACC	ACT
rs2413391	TGATATGTT CAGCGGTGCAC	ACT
rs132749	TCTTGATGTTTCTCCTATCCC	ACG
rs132750	CCTGTGGAAACTCAGCAGC	ACG
rs132741	GCACTAGATATTGAATTCTTTCC	ACT
rs2413388	CAACCCCGTGACTGGAGATTC	CGT
rs2413389	TTTCTCTCTCTAGTACTCTATTT	ACT

Genetic Analysis

[0324] Allelotyping results from the discovery cohort are shown for cases and controls in Table 63. The allele frequency for the A2 allele is noted in the fifth and sixth columns for osteoarthritis case pools and control pools, respectively, where “AF” is allele frequency. The allele frequency for the A1 allele can be easily calculated by subtracting the A2 allele frequency from 1 (A1 AF = 1-A2 AF). For example, the SNP rs2010605 has the following case and control allele frequencies: case A1 (A) = 0.19; case A2 (G) = 0.81; control A1 (A) = 0.18; and control A2 (G) = 0.82, where the nucleotide is provided in paranthesis. Some SNPs are labeled “untyped” because of failed assays.

TABLE 63

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3888818	201	34781551	C/T			
rs2010605	425	34781775	A/G	0.81	0.82	0.782
rs743919	1095	34782445	G/T	0.10	0.11	0.502
rs1008134	2201	34783551	A/C			
rs132607	7879	34789229	A/G	0.11	0.11	0.813
rs1476029	8395	34789745	C/T	0.15	0.15	0.983
rs1476030	8461	34789811	C/T	0.36	0.37	0.708
rs2413380	9503	34790853	C/T	0.29	0.29	0.900
rs2051609	10304	34791654	G/T			
rs2413381	10695	34792045	C/T			
rs1894604	16300	34797650	A/G	0.08	0.08	0.759
rs1894605	16444	34797794	G/T	0.08	0.09	0.468
rs132609	17591	34798941	C/T	0.68	0.67	0.777
rs132610	17988	34799338	-/A			
rs132611	19116	34800466	-/T	0.14	0.15	0.863
rs132612	19358	34800708	C/T	0.23	0.23	0.951
rs1008790	20300	34801650	A/G	0.03	0.10	0.007
rs23085	20669	34802019	A/T	0.31	0.32	0.738
rs105161	20891	34802241	A/G	0.76	0.77	0.826
rs132613	21451	34802801	C/T	0.80	0.81	0.619
rs132614	21978	34803328	C/T	0.16	0.14	0.434

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs132615	22785	34804135	C/G	0.32	0.31	0.740
rs132617	24248	34805598	C/T	0.35	0.36	0.825
rs3865724	24770	34806120	C/T	0.65	0.65	0.940
rs2019657	24844	34806194	A/G	0.20	0.20	0.857
rs3865725	25066	34806416	G/T			
rs2019364	25096	34806446	C/T	0.40	0.39	0.767
rs2008383	25309	34806659	A/G	0.18	0.17	0.665
rs3986002	25344	34806694	A/C			
rs3888942	25529	34806879	A/T			
rs3888943	25537	34806887	A/G			
rs3888944	25554	34806904	A/C			
rs132618	27963	34809313	A/T	0.43	0.43	0.934
rs132619	28134	34809484	G/T			
rs3827346	28356	34809706	A/G	0.84	0.84	0.976
rs132620	29648	34810998	-/A	0.29	0.29	0.879
rs132621	29986	34811336	A/G	0.32	0.31	0.867
rs80575	30217	34811567	G/T	0.27	0.27	0.948
rs80576	30267	34811617	A/G	0.26	0.25	0.443
rs80577	30315	34811665	A/G	0.26	0.23	0.191
rs80578	30585	34811935	C/T	0.49	0.48	0.548
rs80579	30724	34812074	A/C	0.23	0.25	0.574
rs80580	30897	34812247	C/T	0.31	0.31	0.878
rs132622	30931	34812281	C/T	0.29	0.30	0.943
rs132623	31080	34812430	G/T	0.60	0.59	0.806
rs132624	31246	34812596	C/T	0.36	0.37	0.772
rs132625	31373	34812723	A/T			
rs132626	31463	34812813	A/G	0.89	0.84	0.082
rs132627	31467	34812817	A/G	0.12	0.11	0.836
rs1807672	32188	34813538	G/T	0.30	0.30	0.974
rs132628	32288	34813638	C/T	0.25	0.24	0.691
rs132629	32520	34813870	A/T	0.04	0.06	0.250
rs132630	32594	34813944	A/C	0.75	0.75	0.978
rs132631	32657	34814007	A/C	0.72	0.73	0.509
rs132632	32677	34814027	A/G	0.66	0.65	0.798
rs132633	32764	34814114	C/T	0.34	0.33	0.796
rs132634	32784	34814134	A/G	0.45	0.42	0.317
rs132635	32830	34814180	C/T	0.41	0.40	0.772
rs132636	32872	34814222	C/T	0.41	0.44	0.192
rs129603	33121	34814471	A/C			
rs132637	33348	34814698	G/T	0.09	0.09	0.628
rs3788518	33952	34815302	C/G	0.17	0.19	0.297
rs132638	34184	34815534	C/G	0.56	0.58	0.509
rs132639	34361	34815711	A/T	0.13	0.12	0.561
rs132640	35026	34816376	A/G	0.32	0.30	0.388
rs132641	35192	34816542	A/G	0.48	0.51	0.287
rs132642	35600	34816950	A/T	0.15	0.14	0.732
rs132643	36033	34817383	C/T	0.44	0.46	0.360
rs132644	36289	34817639	C/T	0.53	0.58	0.075
rs132645	38869	34820219	A/G	0.19	0.18	0.572
rs2017329	39629	34820979	A/T	0.39	0.40	0.915
rs739198	40530	34821880	C/T	0.70	0.70	0.878
rs132647	41621	34822971	C/T	0.23	0.23	0.957
rs2097465	42379	34823729	C/T	0.54	0.51	0.344
rs2105915	42802	34824152	C/T	0.57	0.56	0.468
rs132648	42865	34824215	T/C			
rs132649	43644	34824994	A/G	0.21	0.22	0.579
rs132650	45051	34826401	C/T	0.34	0.31	0.248
rs132651	45828	34827178	A/C			
rs132652	45829	34827179	A/T			
rs80584	46257	34827607	C/T	0.81	0.75	0.043
rs132653	47286	34828636	A/C	0.17	0.15	0.312
rs916334	47427	34828777	C/T	0.34	0.36	0.345
rs132654	47963	34829313	C/T	0.54	0.56	0.439
rs132655	48013	34829363	C/T	0.41	0.41	0.838

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs132656	48229	34829579	C/T	0.37	0.36	0.813
rs3834684	48282	34829632	-/A	0.21	0.22	0.480
rs132657	48376	34829726	-/G	0.49	0.50	0.719
rs916335	48404	34829754	A/G	0.38	0.36	0.509
rs132659	49900	34831250	C/T			
rs132660	52699	34834049	G/T	0.37	0.38	0.754
rs132661	52897	34834247	A/G	0.27	0.29	0.291
rs132662	53414	34834764	A/G	0.61	0.58	0.186
rs132663	53487	34834837	A/T	0.26	0.29	0.167
rs132664	54112	34835462	G/T	0.25	0.29	0.098
rs132667	55492	34836842	A/G	0.35	0.36	0.559
rs132670	59766	34841116	C/T			
rs132671	60307	34841657	A/G	0.49	0.53	0.145
rs132672	60701	34842051	A/G	0.23	0.22	0.716
rs132673	60952	34842302	A/G	0.41	0.37	0.184
rs132674	61401	34842751	C/T	0.32	0.31	0.476
rs132675	62379	34843729	C/T	0.38	0.35	0.188
rs80585	62870	34844220	C/T	0.28	0.27	0.525
rs80586	62879	34844229	A/G	0.66	0.66	0.966
rs132676	63499	34844849	A/T	0.26	0.23	0.177
rs132677	64284	34845634	-/A	0.69	0.69	0.873
rs132678	64408	34845758	A/G	0.46	0.48	0.395
rs132680	64760	34846110	A/G	0.20	0.20	0.995
rs132681	65230	34846580	A/G	0.24	0.24	0.901
rs132683	66127	34847477	A/G	0.19	0.19	0.851
rs2269594	66634	34847984	C/T	0.70	0.67	0.332
rs132684	66686	34848036	A/G	0.21	0.20	0.756
rs132685	66694	34848044	C/G	0.30	0.28	0.553
rs132686	67113	34848463	A/G	0.46	0.48	0.398
rs132687	67257	34848607	A/G	0.96	0.96	0.767
rs132688	67403	34848753	A/G	0.24	0.23	0.553
rs132689	67609	34848959	A/G	0.61	0.63	0.564
rs132690	68418	34849768	-/A	0.16	0.17	0.672
rs132691	68610	34849960	C/G	0.52	0.52	0.976
rs132692	69629	34850979	C/T	0.63	0.62	0.800
rs132693	70024	34851374	A/G	0.58	0.58	0.868
rs132694	70848	34852198	A/G	0.17	0.16	0.583
rs132695	71428	34852778	C/G	0.23	0.22	0.616
rs1966266	71553	34852903	C/T	0.49	0.47	0.413
rs1966267	71633	34852983	A/G	0.40	0.41	0.773
rs106808	71768	34853118	A/C	0.68	0.67	0.617
rs132696	71769	34853119	A/G			
rs2239829	73039	34854389	A/G	0.34	0.36	0.510
rs2285154	73325	34854675	A/G			
rs2239830	73412	34854762	A/C	0.49	0.50	0.841
rs2239831	73547	34854897	C/T	0.52	0.50	0.564
rs3865722	73769	34855119	A/T	0.57	0.56	0.861
rs3865723	73806	34855156	A/G	0.59	0.58	0.722
rs3985996	74467	34855817	C/T	0.30	0.29	0.861
rs3985997	74472	34855822	C/T	0.89	0.90	0.527
rs3985998	74473	34855823	A/G			
rs3985999	74482	34855832	C/T	0.19	0.19	0.968
rs3986000	74494	34855844	A/C			
rs2413382	74592	34855942	A/G	0.61	0.59	0.618
rs2413383	74670	34856020	G/T			
rs2413384	74672	34856022	G/T			
rs2413385	74714	34856064	G/T	0.70	0.70	0.944
rs2413386	74723	34856073	A/T	0.70	0.71	0.816
rs1894606	74749	34856099	A/G			
rs916336	74861	34856211	C/G			
rs916337	74892	34856242	C/T			
rs916338	74893	34856243	C/T	0.40	0.40	0.939
rs132697	75176	34856526	A/G	0.59	0.61	0.418
rs12781	75705	34857055	A/G			

dBSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs1053983	75989	34857339	A/G	0.42	0.43	0.848
rs1053982	76027	34857377	A/G	0.69	0.69	0.981
rs2227167	77949	34859299	A/G	0.35	0.37	0.392
rs2227168	77974	34859324	C/T	0.38	0.38	0.797
rs132700	78167	34859517	C/T	0.25	0.25	0.729
rs3075364	78310	34859660	-JCT	0.42	0.42	0.879
rs2227169	78415	34859765	C/T	0.38	0.37	0.619
rs2097466	78575	34859925	C/T	0.52	0.52	0.962
rs2097467	78590	34859940	C/T			
rs2413387	78709	34860059	C/T			
rs132701	78875	34860225	C/T	0.23	0.23	0.951
rs132702	79864	34861214	C/T			
rs132703	81316	34862666	C/T	0.52	0.52	0.995
rs2269595	81320	34862670	A/G	0.19	0.18	0.464
rs2269596	81409	34862759	C/T	0.40	0.40	0.753
rs132704	81737	34863087	C/T	0.65	0.66	0.906
rs2007468	81843	34863193	A/G	0.40	0.40	0.987
rs132705	82102	34863452	C/T	0.30	0.30	0.944
rs2007706	82833	34864183	C/T	0.32	0.32	0.944
rs132706	83461	34864811	C/T			
rs132707	83624	34864974	C/T	0.26	0.28	0.540
rs132708	83660	34865010	C/G	0.30	0.29	0.506
rs132709	83701	34865051	A/T	0.45	0.46	0.538
rs132710	83708	34865058	A/G	0.62	0.60	0.310
rs132711	83782	34865132	C/T			
rs132712	85707	34867057	A/G	0.84	0.84	0.693
rs132713	85717	34867067	A/G	0.29	0.30	0.911
rs132714	86486	34867836	C/T			
rs132716	86833	34868183	A/G			
rs132717	87115	34868465	C/T	0.48	0.49	0.647
rs132718	87234	34868584	A/G	0.68	0.69	0.453
rs132719	87479	34868829	G/T	0.59	0.54	0.078
rs132720	87561	34868911	A/G	0.12	0.13	0.607
rs132721	87604	34868954	A/G	0.73	0.73	0.919
rs132722	87674	34869024	C/T	0.22	0.22	0.985
rs132723	87958	34869308	A/G	0.03	NA	0.033
rs132724	87992	34869342	-/G	0.12	0.12	0.830
rs132725	88019	34869369	A/G	0.69	0.64	0.097
rs132726	88074	34869424	C/G	0.10	0.13	0.240
rs132727	88079	34869429	C/G	0.68	0.67	0.865
rs132728	88115	34869465	A/G			
rs132729	88118	34869468	C/G			
rs132730	88120	34869470	A/G			
rs132731	88135	34869485	-/CTCAT			
rs132732	88142	34869492	G/T			
rs132733	88143	34869493	G/T			
rs140575	88149	34869499	ACA/TG	0.37	0.38	0.656
rs132734	88340	34869690	A/G	0.46	0.44	0.522
rs132735	88344	34869694	G/T	0.85	0.85	0.781
rs80587	88512	34869862	C/G	0.40	0.42	0.493
rs132736	88521	34869871	C/T			
rs132737	88650	34870000	C/G	0.32	0.33	0.824
rs132738	88827	34870177	C/T	0.78	0.80	0.327
rs1807673	89230	34870580	A/G	0.28	0.28	0.969
rs2014700	89236	34870586	A/G	0.89	0.92	0.036
rs132739	90754	34872104	G/A			
rs1812023	90984	34872334	A/G	0.70	0.70	0.997
rs1812024	91110	34872460	A/G	0.68	0.69	0.755
rs2005590	92026	34873376	C/T	0.71	0.73	0.252
rs132740	92954	34874304	C/T	0.09	0.08	0.370
rs3986001	93375	34874725	-/TTGC	0.51	0.54	0.302
rs2413390	93794	34875144	C/T	0.37	0.41	0.103
rs132743	94937	34876287	C/G	0.07	0.07	0.985
rs132744	95068	34876418	C/T	0.73	0.78	0.078

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs2413391	96188	34877538	A/G	0.39	0.40	0.938
rs132749	97092	34878442	C/T	0.47	0.50	0.329
rs132750	98812	34880162	C/T	0.67	0.67	0.710
rs132741	not mapped	not mapped	A/C	0.29	0.30	0.608
rs2413388	not mapped	not mapped	A/T	0.31	0.31	0.967
rs2413389	not mapped	not mapped	C/G	0.30	0.28	0.393

[0325] The *APOL3* proximal SNPs were also allelotyped in the replication cohorts using the methods described herein and the primers provided in Tables 61 and 62. The replication allelotyping results for replication cohort #1 and replication cohort #2 are provided in Tables 64 and 65, respectively.

TABLE 64

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3888818	201	34781551	C/T			
rs2010605	425	34781775	A/G	0.79	0.80	0.664
rs743919	1095	34782445	G/T	0.11	0.11	0.982
rs1008134	2201	34783551	A/C			
rs132607	7879	34789229	A/G	0.10	0.11	0.589
rs1476029	8395	34789745	C/T	0.16	0.13	0.177
rs1476030	8461	34789811	C/T	0.33	0.38	0.149
rs2413380	9503	34790853	C/T	0.26	0.30	0.174
rs2051609	10304	34791654	G/T			
rs2413381	10695	34792045	C/T			
rs1894604	16300	34797650	A/G	0.07	0.08	0.476
rs1894605	16444	34797794	G/T	0.07	0.09	0.269
rs132609	17591	34798941	C/T	0.68	0.67	0.687
rs132610	17988	34799338	-/A			
rs132611	19116	34800466	-/T	0.14	0.14	0.992
rs132612	19358	34800708	C/T	0.22	0.22	0.799
rs1008790	20300	34801650	A/G	0.03	0.06	0.358
rs23085	20669	34802019	A/T	0.31	0.30	0.868
rs105161	20891	34802241	A/G	0.75	0.80	0.058
rs132613	21451	34802801	C/T	0.82	0.81	0.725
rs132614	21978	34803328	C/T	0.15	0.15	0.914
rs132615	22785	34804135	C/G	0.32	0.32	0.885
rs132617	24248	34805598	C/T	0.36	0.37	0.706
rs3865724	24770	34806120	C/T	0.66	0.64	0.473
rs2019657	24844	34806194	A/G	0.21	0.21	0.898
rs3865725	25066	34806416	G/T			
rs2019364	25096	34806446	C/T	0.41	0.39	0.480
rs2008383	25309	34806659	A/G	0.17	0.16	0.721
rs3986002	25344	34806694	A/C			
rs3888942	25529	34806879	A/T			
rs3888943	25537	34806887	A/G			
rs3888944	25554	34806904	A/C			
rs132618	27963	34809313	A/T	0.42	0.45	0.522
rs132619	28134	34809484	G/T			
rs3827346	28356	34809706	A/G	0.85	0.84	0.703
rs132620	29648	34810998	-/A	0.29	0.28	0.917
rs132621	29986	34811336	A/G	0.32	0.31	0.864
rs80575	30217	34811567	G/T	0.27	0.27	0.909
rs80576	30267	34811617	A/G	0.30	0.22	0.007
rs80577	30315	34811665	A/G	0.24	0.23	0.853
rs80578	30585	34811935	C/T	0.49	0.49	0.884
rs80579	30724	34812074	A/C	0.24	0.25	0.761
rs80580	30897	34812247	C/T	0.30	0.30	0.815
rs132622	30931	34812281	C/T	0.29	0.28	0.884
rs132623	31080	34812430	G/T	0.62	0.63	0.633

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs132624	31246	34812596	C/T	0.36	0.35	0.769
rs132625	31373	34812723	A/T			
rs132626	31463	34812813	A/G	0.92	NA	NA
rs132627	31467	34812817	A/G	0.10	0.10	0.844
rs1807672	32188	34813538	G/T	0.29	0.29	0.954
rs132628	32288	34813638	C/T	0.24	0.25	0.796
rs132629	32520	34813870	A/T	0.03	0.06	0.345
rs132630	32594	34813944	A/C	0.75	0.72	0.388
rs132631	32657	34814007	A/C	0.70	0.77	0.017
rs132632	32677	34814027	A/G	0.67	0.63	0.275
rs132633	32764	34814114	C/T	0.34	0.32	0.558
rs132634	32784	34814134	A/G	0.44	0.41	0.435
rs132635	32830	34814180	C/T	0.39	NA	0.409
rs132636	32872	34814222	C/T	0.42	0.46	0.179
rs129603	33121	34814471	A/C			
rs132637	33348	34814698	G/T	0.08	0.10	0.462
rs3788518	33952	34815302	C/G	0.19	0.19	0.855
rs132638	34184	34815534	C/G	0.54	0.60	0.114
rs132639	34361	34815711	A/T	0.13	0.09	0.153
rs132640	35026	34816376	A/G	0.31	0.32	0.767
rs132641	35192	34816542	A/G	0.46	0.53	0.074
rs132642	35600	34816950	A/T	0.16	0.12	0.101
rs132643	36033	34817383	C/T	0.42	0.48	0.081
rs132644	36289	34817639	C/T	0.50	0.62	~0.0001
rs132645	38869	34820219	A/G	0.21	0.15	0.027
rs2017329	39629	34820979	A/T	0.40	0.38	0.737
rs739198	40530	34821880	C/T	0.74	NA	0.697
rs132647	41621	34822971	C/T	0.21	0.24	0.430
rs2097465	42379	34823729	C/T	0.54	0.52	0.670
rs2105915	42802	34824152	C/T	0.57	0.55	0.582
rs132648	42865	34824215	T/C			
rs132649	43644	34824994	A/G	0.20	0.23	0.213
rs132650	45051	34826401	C/T	0.36	0.29	0.033
rs132651	45828	34827178	A/C			
rs132652	45829	34827179	A/T			
rs80584	46257	34827607	C/T	0.81	0.75	0.043
rs132653	47286	34828636	A/C	0.18	0.13	0.060
rs916334	47427	34828777	C/T	0.32	0.38	0.064
rs132654	47963	34829313	C/T	0.55	0.54	0.769
rs132655	48013	34829363	C/T	0.42	0.39	0.390
rs132656	48229	34829579	C/T	0.38	0.35	0.429
rs3834684	48282	34829632	-A	0.21	0.23	0.416
rs132657	48376	34829726	-G	0.47	0.53	0.089
rs916335	48404	34829754	A/G	0.39	0.33	0.153
rs132659	49900	34831250	C/T			
rs132660	52699	34834049	G/T	0.39	0.36	0.227
rs132661	52897	34834247	A/G	0.25	0.31	0.086
rs132662	53414	34834764	A/G	0.63	0.57	0.083
rs132663	53487	34834837	A/T	0.25	0.31	0.051
rs132664	54112	34835462	G/T	0.23	0.29	0.037
rs132667	55492	34836842	A/G	0.34	0.32	0.546
rs132670	59766	34841116	C/T			
rs132671	60307	34841657	A/G	0.49	0.55	0.041
rs132672	60701	34842051	A/G	0.24	0.20	0.211
rs132673	60952	34842302	A/G	0.40	0.36	0.284
rs132674	61401	34842751	C/T	0.32	0.29	0.453
rs132675	62379	34843729	C/T	0.38	0.33	0.178
rs80585	62870	34844220	C/T	0.29	0.24	0.164
rs80586	62879	34844229	A/G	0.65	0.69	0.212
rs132676	63499	34844849	A/T	0.26	0.20	0.034
rs132677	64284	34845634	-A	0.69	0.72	0.438
rs132678	64408	34845758	A/G	0.48	0.50	0.572
rs132680	64760	34846110	A/G	0.20	0.18	0.429
rs132681	65230	34846580	A/G	0.25	0.22	0.362

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs132683	66127	34847477	A/G	0.19	0.17	0.449
rs2269594	66634	34847984	C/T	0.70	0.65	0.234
rs132684	66686	34848036	A/G	0.21	0.18	0.349
rs132685	66694	34848044	C/G	0.30	0.28	0.528
rs132686	67113	34848463	A/G	0.46	0.50	0.207
rs132687	67257	34848607	A/G	0.95	0.98	0.217
rs132688	67403	34848753	A/G	0.26	0.23	0.367
rs132689	67609	34848959	A/G	0.60	0.63	0.353
rs132690	68418	34849768	-/A	0.16	0.15	0.901
rs132691	68610	34849960	C/G	0.51	0.53	0.573
rs132692	69629	34850979	C/T	0.62	0.64	0.566
rs132693	70024	34851374	A/G	0.58	0.62	0.227
rs132694	70848	34852198	A/G	0.17	0.14	0.195
rs132695	71428	34852778	C/G	0.24	0.22	0.560
rs1966266	71553	34852903	C/T	0.49	0.46	0.389
rs1966267	71633	34852983	A/G	0.40	0.43	0.304
rs106808	71768	34853118	A/C	0.66	0.70	0.243
rs132696	71769	34853119	A/G			
rs2239829	73039	34854389	A/G	0.34	0.38	0.264
rs2285154	73325	34854675	A/G			
rs2239830	73412	34854762	A/C	0.49	NA	0.490
rs2239831	73547	34854897	C/T	0.52	0.48	0.254
rs3865722	73769	34855119	A/T	0.57	0.56	0.739
rs3865723	73806	34855156	A/G	0.58	0.57	0.819
rs3985996	74467	34855817	C/T	0.30	0.31	0.799
rs3985997	74472	34855822	C/T	0.88	0.89	0.941
rs3985998	74473	34855823	A/G			
rs3985999	74482	34855832	C/T	0.20	0.20	0.871
rs3986000	74494	34855844	A/C			
rs2413382	74592	34855942	A/G	0.61	0.58	0.311
rs2413383	74670	34856020	G/T			
rs2413384	74672	34856022	G/T			
rs2413385	74714	34856064	G/T	0.70	0.68	0.509
rs2413386	74723	34856073	A/T	0.71	0.70	0.807
rs1894606	74749	34856099	A/G			
rs916336	74861	34856211	C/G			
rs916337	74892	34856242	C/T			
rs916338	74893	34856243	C/T	0.41	0.39	0.465
rs132697	75176	34856526	A/G	0.58	0.63	0.101
rs12781	75705	34857055	A/G			
rs1053983	75989	34857339	A/G	0.41	0.45	0.301
rs1053982	76027	34857377	A/G	0.66	0.66	0.959
rs2227167	77949	34859299	A/G	0.35	0.39	0.313
rs2227168	77974	34859324	C/T	0.39	0.35	0.234
rs132700	78167	34859517	C/T	0.26	0.24	0.652
rs3075364	78310	34859660	-/CT	0.42	0.45	0.287
rs2227169	78415	34859765	C/T	0.40	0.36	0.293
rs2097466	78575	34859925	C/T	0.52	0.49	0.376
rs2097467	78590	34859940	C/T			
rs2413387	78709	34860059	C/T			
rs132701	78875	34860225	C/T	0.23	0.21	0.499
rs132702	79864	34861214	C/T			
rs132703	81316	34862666	C/T	0.52	0.52	0.995
rs2269595	81320	34862670	A/G	0.20	0.17	0.210
rs2269596	81409	34862759	C/T	0.42	0.37	0.172
rs132704	81737	34863087	C/T	0.64	0.67	0.398
rs2007468	81843	34863193	A/G	0.39	0.42	0.354
rs132705	82102	34863452	C/T	0.29	0.28	0.834
rs2007706	82833	34864183	C/T	0.29	0.27	0.546
rs132706	83461	34864811	C/T			
rs132707	83624	34864974	C/T	0.26	0.29	0.252
rs132708	83660	34865010	C/G	0.29	0.28	0.584
rs132709	83701	34865051	A/T	0.46	0.47	0.748
rs132710	83708	34865058	A/G	0.62	0.60	0.477

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs132711	83782	34865132	C/T			
rs132712	85707	34867057	A/G	0.82	0.82	0.984
rs132713	85717	34867067	A/G	0.31	0.33	0.416
rs132714	86486	34867836	C/T			
rs132716	86833	34868183	A/G			
rs132717	87115	34868465	C/T	0.48	NA	NA
rs132718	87234	34868584	A/G	0.67	0.71	0.237
rs132719	87479	34868829	G/T	0.56	0.52	0.254
rs132720	87561	34868911	A/G	0.12	0.14	0.416
rs132721	87604	34868954	A/G	0.72	0.71	0.626
rs132722	87674	34869024	C/T	0.23	0.24	0.791
rs132723	87958	34869308	A/G	NA	NA	
rs132724	87992	34869342	-/G	0.12	0.12	0.830
rs132725	88019	34869369	A/G	0.60	NA	0.691
rs132726	88074	34869424	C/G	0.09	0.15	0.103
rs132727	88079	34869429	C/G	0.68	0.66	0.536
rs132728	88115	34869465	A/G			
rs132729	88118	34869468	C/G			
rs132730	88120	34869470	A/G			
rs132731	88135	34869485	-/CTCAT			
rs132732	88142	34869492	G/T			
rs132733	88143	34869493	G/T			
rs140575	88149	34869499	ACA/TG	0.43	0.44	0.792
rs132734	88340	34869690	A/G	0.45	0.41	0.263
rs132735	88344	34869694	G/T	0.83	0.82	0.629
rs80587	88512	34869862	C/G	0.42	0.47	0.152
rs132736	88521	34869871	C/T			
rs132737	88650	34870000	C/G	0.33	0.35	0.631
rs132738	88827	34870177	C/T	0.74	0.79	0.131
rs1807673	89230	34870580	A/G	0.30	0.32	0.583
rs2014700	89236	34870586	A/G	0.85	0.90	0.043
rs132739	90754	34872104	G/A			
rs1812023	90984	34872334	A/G	0.70	NA	0.704
rs1812024	91110	34872460	A/G	0.66	0.68	0.563
rs2005590	92026	34873376	C/T	0.72	0.75	0.268
rs132740	92954	34874304	C/T	0.10	0.06	0.085
rs3986001	93375	34874725	-/TTGC	0.49	0.53	0.341
rs2413390	93794	34875144	C/T	0.35	0.40	0.143
rs132743	94937	34876287	C/G	0.06	0.05	0.608
rs132744	95068	34876418	C/T	0.72	0.78	0.069
rs2413391	96188	34877538	A/G	0.37	0.39	0.544
rs132749	97092	34878442	C/T	0.48	0.51	0.311
rs132750	98812	34880162	C/T	0.65	0.67	0.678
rs132741	not mapped	not mapped	A/C	0.28	0.30	0.509
rs2413388	not mapped	not mapped	A/T	0.32	0.32	0.908
rs2413389	not mapped	not mapped	C/G	0.32	0.29	0.480

TABLE 65

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs3888818	201	34781551	C/T			
rs2010605	425	34781775	A/G	0.84	0.84	0.924
rs743919	1095	34782445	G/T	0.08	0.11	0.294
rs1008134	2201	34783551	A/C			
rs132607	7879	34789229	A/G	0.13	0.10	0.297
rs1476029	8395	34789745	C/T	0.13	0.18	0.126
rs1476030	8461	34789811	C/T	0.40	0.35	0.214
rs2413380	9503	34790853	C/T	0.33	0.28	0.163
rs2051609	10304	34791654	G/T			
rs2413381	10695	34792045	C/T			
rs1894604	16300	34797650	A/G	0.09	0.08	0.726
rs1894605	16444	34797794	G/T	0.09	0.09	0.834

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs132609	17591	34798941	C/T	0.67	0.67	0.950
rs132610	17988	34799338	-/A			
rs132611	19116	34800466	-/T	0.14	0.15	0.749
rs132612	19358	34800708	C/T	0.23	0.24	0.780
rs1008790	20300	34801650	A/G	untyped	0.16	NA
rs23085	20669	34802019	A/T	0.32	0.35	0.395
rs105161	20891	34802241	A/G	0.78	0.71	0.037
rs132613	21451	34802801	C/T	0.78	0.82	0.245
rs132614	21978	34803328	C/T	0.17	0.13	0.167
rs132615	22785	34804135	C/G	0.31	0.30	0.691
rs132617	24248	34805598	C/T	0.35	0.35	0.862
rs3865724	24770	34806120	C/T	0.64	0.67	0.384
rs2019657	24844	34806194	A/G	0.17	0.18	0.745
rs3865725	25066	34806416	G/T			
rs2019364	25096	34806446	C/T	0.38	0.39	0.702
rs2008383	25309	34806659	A/G	0.18	0.18	0.853
rs3986002	25344	34806694	A/C			
rs3888942	25529	34806879	A/T			
rs3888943	25537	34806887	A/G			
rs3888944	25554	34806904	A/C			
rs132618	27963	34809313	A/T	0.44	0.40	0.330
rs132619	28134	34809484	G/T			
rs3827346	28356	34809706	A/G	0.84	0.85	0.568
rs132620	29648	34810998	-/A	0.30	0.31	0.665
rs132621	29986	34811336	A/G	0.32	0.32	0.955
rs80575	30217	34811567	G/T	0.26	0.27	0.812
rs80576	30267	34811617	A/G	0.22	0.29	0.024
rs80577	30315	34811665	A/G	0.27	0.21	0.072
rs80578	30585	34811935	C/T	0.50	0.46	0.263
rs80579	30724	34812074	A/C	0.22	0.24	0.639
rs80580	30897	34812247	C/T	0.32	0.32	0.976
rs132622	30931	34812281	C/T	0.30	0.32	0.701
rs132623	31080	34812430	G/T	0.57	0.52	0.224
rs132624	31246	34812596	C/T	0.36	0.39	0.393
rs132625	31373	34812723	A/T			
rs132626	31463	34812813	A/G	0.86	0.84	0.723
rs132627	31467	34812817	A/G	0.14	0.12	0.672
rs1807672	32188	34813538	G/T	0.31	0.31	0.940
rs132628	32288	34813638	C/T	0.26	0.23	0.307
rs132629	32520	34813870	A/T	0.05	0.07	0.493
rs132630	32594	34813944	A/C	0.76	0.80	0.269
rs132631	32657	34814007	A/C	0.74	0.67	0.058
rs132632	32677	34814027	A/G	0.64	0.68	0.316
rs132633	32764	34814114	C/T	0.33	0.34	0.757
rs132634	32784	34814134	A/G	0.45	0.43	0.574
rs132635	32830	34814180	C/T	0.42	-0.01	
rs132636	32872	34814222	C/T	0.40	0.40	0.856
rs129603	33121	34814471	A/C			
rs132637	33348	34814698	G/T	0.09	0.09	0.882
rs3788518	33952	34815302	C/G	0.15	0.19	0.133
rs132638	34184	34815534	C/G	0.58	0.55	0.324
rs132639	34361	34815711	A/T	0.13	0.16	0.210
rs132640	35026	34816376	A/G	0.34	0.28	0.075
rs132641	35192	34816542	A/G	0.49	0.47	0.539
rs132642	35600	34816950	A/T	0.14	0.19	0.079
rs132643	36033	34817383	C/T	0.47	0.45	0.565
rs132644	36289	34817639	C/T	0.57	0.51	0.156
rs132645	38869	34820219	A/G	0.17	0.23	0.076
rs2017329	39629	34820979	A/T	0.39	0.42	0.531
rs739198	40530	34821880	C/T	0.64	0.05	
rs132647	41621	34822971	C/T	0.25	0.22	0.339
rs2097465	42379	34823729	C/T	0.54	0.50	0.311
rs2105915	42802	34824152	C/T	0.58	0.56	0.667
rs132648	42865	34824215	T/C			

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs132649	43644	34824994	A/G	0.21	0.19	0.471
rs132650	45051	34826401	C/T	0.31	0.34	0.365
rs132651	45828	34827178	A/C			
rs132652	45829	34827179	A/T			
rs80584	46257	34827607	C/T			
rs132653	47286	34828636	A/C	0.15	0.18	0.404
rs916334	47427	34828777	C/T	0.36	0.33	0.383
rs132654	47963	34829313	C/T	0.53	0.60	0.090
rs132655	48013	34829363	C/T	0.39	0.44	0.150
rs132656	48229	34829579	C/T	0.36	0.39	0.507
rs3834684	48282	34829632	-/A	0.21	0.21	0.956
rs132657	48376	34829726	-/G	0.51	0.45	0.112
rs916335	48404	34829754	A/G	0.36	0.40	0.245
rs132659	49900	34831250	C/T			
rs132660	52699	34834049	G/T	0.33	0.41	0.044
rs132661	52897	34834247	A/G	0.29	0.27	0.624
rs132662	53414	34834764	A/G	0.59	0.59	0.998
rs132663	53487	34834837	A/T	0.27	0.26	0.792
rs132664	54112	34835462	G/T	0.28	0.28	0.934
rs132667	55492	34836842	A/G	0.36	0.42	0.054
rs132670	59766	34841116	C/T			
rs132671	60307	34841657	A/G	0.50	0.49	0.839
rs132672	60701	34842051	A/G	0.21	0.25	0.297
rs132673	60952	34842302	A/G	0.42	0.40	0.525
rs132674	61401	34842751	C/T	0.33	0.32	0.909
rs132675	62379	34843729	C/T	0.38	0.36	0.722
rs80585	62870	34844220	C/T	0.27	0.30	0.405
rs80586	62879	34844229	A/G	0.68	0.62	0.113
rs132676	63499	34844849	A/T	0.25	0.27	0.442
rs132677	64284	34845634	-/A	0.69	0.64	0.147
rs132678	64408	34845758	A/G	0.43	0.45	0.620
rs132680	64760	34846110	A/G	0.19	0.23	0.258
rs132681	65230	34846580	A/G	0.23	0.28	0.201
rs132683	66127	34847477	A/G	0.19	0.21	0.493
rs2269594	66634	34847984	C/T	0.68	0.69	0.866
rs132684	66686	34848036	A/G	0.21	0.24	0.487
rs132685	66694	34848044	C/G	0.29	0.29	0.888
rs132686	67113	34848463	A/G	0.45	0.44	0.708
rs132687	67257	34848607	A/G	0.96	0.93	0.210
rs132688	67403	34848753	A/G	0.22	0.23	0.917
rs132689	67609	34848959	A/G	0.63	0.62	0.839
rs132690	68418	34849768	-/A	0.16	0.19	0.295
rs132691	68610	34849960	C/G	0.53	0.50	0.441
rs132692	69629	34850979	C/T	0.64	0.59	0.223
rs132693	70024	34851374	A/G	0.57	0.52	0.191
rs132694	70848	34852198	A/G	0.17	0.20	0.413
rs132695	71428	34852778	C/G	0.23	0.23	0.928
rs1966266	71553	34852903	C/T	0.49	0.49	0.881
rs1966267	71633	34852983	A/G	0.41	0.38	0.400
rs106808	71768	34853118	A/C	0.71	0.63	0.030
rs132696	71769	34853119	A/G			
rs2239829	73039	34854389	A/G	0.35	0.33	0.665
rs2285154	73325	34854675	A/G			
rs2239830	73412	34854762	A/C	0.51	-0.02	
rs2239831	73547	34854897	C/T	0.51	0.53	0.577
rs3865722	73769	34855119	A/T	0.56	0.57	0.887
rs3865723	73806	34855156	A/G	0.61	0.60	0.837
rs3985996	74467	34855817	C/T	0.30	0.27	0.501
rs3985997	74472	34855822	C/T	0.89	0.92	0.287
rs3985998	74473	34855823	A/G			
rs3985999	74482	34855832	C/T	0.18	0.17	0.691
rs3986000	74494	34855844	A/C			
rs2413382	74592	34855942	A/G	0.60	0.62	0.642
rs2413383	74670	34856020	G/T			

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs2413384	74672	34856022	G/T			
rs2413385	74714	34856064	G/T	0.70	0.72	0.433
rs2413386	74723	34856073	A/T	0.70	0.72	0.510
rs1894606	74749	34856099	A/G			
rs916336	74861	34856211	C/G			
rs916337	74892	34856242	C/T			
rs916338	74893	34856243	C/T	0.39	0.43	0.334
rs132697	75176	34856526	A/G	0.60	0.57	0.463
rs12781	75705	34857055	A/G			
rs1053983	75989	34857339	A/G	0.43	0.39	0.279
rs1053982	76027	34857377	A/G	0.74	0.74	0.852
rs2227167	77949	34859299	A/G	0.35	0.35	0.998
rs2227168	77974	34859324	C/T	0.38	0.42	0.226
rs132700	78167	34859517	C/T	0.25	0.25	0.989
rs3075364	78310	34859660	-/CT	0.41	0.37	0.252
rs2227169	78415	34859765	C/T	0.36	0.38	0.520
rs2097466	78575	34859925	C/T	0.52	0.57	0.255
rs2097467	78590	34859940	C/T			
rs2413387	78709	34860059	C/T			
rs132701	78875	34860225	C/T	0.23	0.27	0.255
rs132702	79864	34861214	C/T			
rs132703	81316	34862666	C/T			
rs2269595	81320	34862670	A/G	0.18	0.19	0.672
rs2269596	81409	34862759	C/T	0.39	0.43	0.258
rs132704	81737	34863087	C/T	0.67	0.64	0.391
rs2007468	81843	34863193	A/G	0.41	0.37	0.247
rs132705	82102	34863452	C/T	0.32	0.33	0.785
rs2007706	82833	34864183	C/T	0.36	0.41	0.226
rs132706	83461	34864811	C/T			
rs132707	83624	34864974	C/T	0.27	0.26	0.598
rs132708	83660	34865010	C/G	0.31	0.30	0.754
rs132709	83701	34865051	A/T	0.43	0.45	0.627
rs132710	83708	34865058	A/G	0.63	0.60	0.482
rs132711	83782	34865132	C/T			
rs132712	85707	34867057	A/G	0.87	0.86	0.667
rs132713	85717	34867067	A/G	0.28	0.24	0.293
rs132714	86486	34867836	C/T			
rs132716	86833	34868183	A/G			
rs132717	87115	34868465	C/T	0.47	0.49	0.533
rs132718	87234	34868584	A/G	0.68	0.66	0.705
rs132719	87479	34868829	G/T	0.62	0.57	0.223
rs132720	87561	34868911	A/G	0.12	0.11	0.727
rs132721	87604	34868954	A/G	0.75	0.77	0.495
rs132722	87674	34869024	C/T	0.21	0.20	0.630
rs132723	87958	34869308	A/G			
rs132724	87992	34869342	-/G			
rs132725	88019	34869369	A/G	0.69	0.00	
rs132726	88074	34869424	C/G	0.12	0.10	0.509
rs132727	88079	34869429	C/G	0.68	0.70	0.583
rs132728	88115	34869465	A/G			
rs132729	88118	34869468	C/G			
rs132730	88120	34869470	A/G			
rs132731	88135	34869485	- /CTCAT			
rs132732	88142	34869492	G/T			
rs132733	88143	34869493	G/T			
rs140575	88149	34869499	ACA/TG	0.30	0.29	0.903
rs132734	88340	34869690	A/G	0.47	0.49	0.571
rs132735	88344	34869694	G/T	0.88	0.90	0.595
rs80587	88512	34869862	C/G	0.37	0.33	0.365
rs132736	88521	34869871	C/T			
rs132737	88650	34870000	C/G	0.31	0.29	0.686
rs132738	88827	34870177	C/T	0.82	0.81	0.773
rs1807673	89230	34870580	A/G	0.26	0.23	0.356

dbSNP rs#	Position in SEQ ID NO: 13	Chromosome Position	A1/A2 Allele	F A2 Case AF	F A2 Control AF	F p- Value
rs2014700	89236	34870586	A/G	0.93	0.96	0.324
rs132739	90754	34872104	G/A			
rs1812023	90984	34872334	A/G	0.71	-0.01	
rs1812024	91110	34872460	A/G	0.70	0.70	0.888
rs2005590	92026	34873376	C/T	0.69	0.70	0.719
rs132740	92954	34874304	C/T	0.08	0.09	0.442
rs3986001	93375	34874725	-/TTGC	0.53	0.55	0.563
rs2413390	93794	34875144	C/T	0.40	0.43	0.365
rs132743	94937	34876287	C/G	0.07	0.09	0.436
rs132744	95068	34876418	C/T	0.74	untyped	
rs2413391	96188	34877538	A/G	0.43	0.41	0.611
rs132749	97092	34878442	C/T	0.47	0.48	0.858
rs132750	98812	34880162	C/T	0.70	0.67	0.285
rs132741	not mapped	not mapped	A/C	0.30	0.30	0.999
rs2413388	not mapped	not mapped	A/T	0.30	0.30	0.989
rs2413389	not mapped	not mapped	C/G	0.28	0.26	0.555

[0326] Allelotyping results were considered particularly significant with a calculated p-value of less than or equal to 0.05 for allelotype results. These values are indicated in bold. The allelotyping p-values were plotted in Figure 1J for the discovery cohort. The position of each SNP on the chromosome is presented on the x-axis. The y-axis provides the negative logarithm (base 10) of the p-value comparing the estimated allele in the case group to that of the control group. The minor allele frequency of the control group for each SNP designated by an X or other symbol on the graph in Figure 1J can be determined by consulting Table 63. For example, the left-most X on the left graph is at position 34781551. By proceeding down the Table from top to bottom and across the graphs from left to right the allele frequency associated with each symbol shown can be determined.

[0327] To aid the interpretation, multiple lines have been added to the graph. The broken horizontal lines are drawn at two common significance levels, 0.05 and 0.01. The vertical broken lines are drawn every 20kb to assist in the interpretation of distances between SNPs. Two other lines are drawn to expose linear trends in the association of SNPs to the disease. The generally bottom-most curve is a nonlinear smoother through the data points on the graph using a local polynomial regression method (W.S. Cleveland, E. Grosse and W.M. Shyu (1992) Local regression models. Chapter 8 of Statistical Models in S eds J.M. Chambers and T.J. Hastie, Wadsworth & Brooks/Cole.). The black line provides a local test for excess statistical significance to identify regions of association. This was created by use of a 10kb sliding window with 1kb step sizes. Within each window, a chi-square goodness of fit test was applied to compare the proportion of SNPs that were significant at a test wise level of 0.01, to the proportion that would be expected by chance alone (0.05 for the methods used here). Resulting p-values that were less than 10^{-8} were truncated at that value.

[0328] The exons and introns of the genes in the covered region are plotted below each graph at the appropriate chromosomal positions. The gene boundary is indicated by the broken horizontal line. The exon positions are shown as thick, unbroken bars. An arrow is placed at the 3' end of each gene to show the direction of transcription.

Example 14Effect of *ADAMTS2* Polypeptides on
Biosynthesis of Type II Collagen in Patients with OA

[0329] To investigate the effect of *ADAMTS2* polypeptides on Type II collagen biosynthesis and processing, human articular cartilage from OA patients undergoing joint replacement is harvested, dissected and maintained as described by Nelson *et al.* (1998) *supra*. Type II procollagen levels in osteoarthritic patients and autopsy controls is determined by radioimmunoassay (RIA) as previously described. Allelic variations (*e.g.*, rs398829) are determined for the OA patients and controls by genotyping (See Examples 1 and 2). As type II procollagen is processed by *ADAMTS2*, increased levels of Type II procollagen in individuals with the allelic variation associated with OA demonstrates that this variation leads to reduced procollagen processing activity and ultimately to OA.

Example 15Effect of *ADAMTS2* Polypeptides on Type II Collagen Processing Activity

[0330] To investigate the effect of *ADAMTS2* polypeptide variants on *ADAMTS2* collagen processing activity, recombinant polypeptides encompassing the *ADAMTS2* variation of SEQ ID NO: 21 at position 733 and a wild-type *ADAMTS2* polypeptide are expressed in cell lines such as chondrocytes. Since the allelic variation of *ADAMTS2* at position 733 of SEQ ID: NO: 21 will prevent the conversion of the *ADAMTS2* pro-enzyme to the catalytically active enzyme, processing of *ADAMTS2* pro-enzyme is monitored by SDS-PAGE analysis followed by Western Blotting using antibodies to *ADAMTS2* and methods common to someone skilled in the art. Reduced levels of pro-enzyme cleavage are apparent by the increased levels of immunopositive protein of higher molecular weight than of the cleaved active protein.

Example 16Gene expression profiling in IL-1 beta and PMA stimulated SW1353 cells

[0331] The human chondrosarcoma cell line, SW1353, (ATCC HTB-94) was grown in L-15 media containing 10% FCS. Culture conditions were at 37 degrees with 0% CO₂ with media changes every 2-3 days. SW1353 cells were grown to 80-90% confluence in 10 cm dishes and then stimulated with either 10ng/ml IL-1 beta (human recombinant, Research Diagnostics) or with 200nm PMA (Sigma). IL-1 beta stimulation was for 3 and 24 hours and PMA stimulation was for 3 and 24 hours. Control cells were grown and extracted in parallel with treated cells. *IL1RL1* was seen to be upregulated by IL1-beta and by phorbol esters in a human chondrocyte cell line model (SW1353 monolayer cell line).

[0332] The expression profiling in IL-1 beta and PMA stimulated SW1353 cells grown in 3-D alginate cultures W1353 cells were cultured as above and then resuspended in 1.2% alginate beads at a density of 4 millions cells/ml according to the manufacturer (Cambrex). Cells were grown for 2 weeks and an alginate bead was removed from culture and tested for the presence of proteoglycans by Alcian Blue staining (Sigma). Positive staining indicated that the chondrocytes were expressing ECM proteins.

Alginate cultures were then stimulated with IL-1 beta for 24 hours or with PMA for 3 hours. Control cells were grown and extracted in parallel with treated cells. *IL1RL1* was seen to be upregulated by IL1-beta and by phorbol esters in a human chondrocyte cell line model (SW1353 3-D alginate cell line).

RNA extraction and cDNA synthesis

[0333] Cells from control chondrocytes and stimulated chondrocytes were isolated at the appropriate time period. mRNA was isolated from total cell lysates using poly dT beads according to the manufacturer (Dyna). Isolated mRNA was used to generate cDNA using SuperScript II reverse transcriptase according to the manufacturer (Invitrogen).

Expression profiling using semi-quantitative PCR

[0334] cDNA levels were normalized using the housekeeping gene, GAPDH. Specific primers corresponding to MMP8 and MMP13 were used in semi-quantitative PCR as positive indicators of induction of an osteoarthritic phenotype. All specific primers used, including MMP8, MMP13, BVES, CHDC1 and *IL1RL1* (transmembrane form, soluble form, soluble isoform 1 and soluble isoform 2) for semi-quantitative PCR and are listed in Table 66.

TABLE 66: Primer Sequences for Expression Profiling

Gene	Forward primer	Reverse primer
GAPDH	ATCATCTCTGCCCCCTCTG	GAGGATTGCTGATGATCTTC
MMP8	CAATACTGGGCTCTGAGTGG	GGAAAGGCACCTGATATGC
MMP13	ATATCTGAACTGGGTCTTCC	GACAGCATCTACTTTATCACC
BVES	AACAGTATAGCCAGCTCC	ATCATCATCTTCTGCTCC
CHDC1	CCAAAGATCAGGACATGGATA	TGCTGTTTGTGGTAGGAGAG
<i>IL1RL1</i> (TM)	CCACTCTGCTCTGGAGAGAC	GCCTGCTCTTTCGTATGTTG
<i>IL1RL1</i> (Sol)	TCCGTCCTGACTCCAAGTT	TTGCTGCTGTGGAATACATG
<i>IL1RL1</i> (ST2_3)	AGGCTTTTCTCTGTTTCC	GTTGAATTCTTGGTTCACC
<i>IL1RL1</i> (ST2_2)	TAATGTGATGACTGAGGACG	TGCAGAACTCTGACACC

[0335] In a human chondrocyte cell line model, *IL1RL1* was seen to be upregulated by IL1-beta and by phorbol esters. *IL1RL1* has an unknown function, but it may possibly mediated inflammatory responses that can contribute to the development of OA. *IL1RL1* is druggable by antibodies or by protein agents.

Example 17

In Vitro Production of Target Polypeptides

[0336] cDNA is cloned into a pIVEX 2.3-MCS vector (Roche Biochem) using a directional cloning method. A cDNA insert is prepared using PCR with forward and reverse primers having 5' restriction site tags (in frame) and 5-6 additional nucleotides in addition to 3' gene-specific portions, the latter of which is typically about twenty to about twenty-five base pairs in length. A Sal I restriction site is introduced by the forward primer and a Sma I restriction site is introduced by the reverse primer. The

ends of PCR products are cut with the corresponding restriction enzymes (*i.e.*, Sal I and Sma I) and the products are gel-purified. The pIVEX 2.3-MCS vector is linearized using the same restriction enzymes, and the fragment with the correct sized fragment is isolated by gel-purification. Purified PCR product is ligated into the linearized pIVEX 2.3-MCS vector and *E. coli* cells transformed for plasmid amplification. The newly constructed expression vector is verified by restriction mapping and used for protein production.

[0337] *E. coli* lysate is reconstituted with 0.25 ml of Reconstitution Buffer, the Reaction Mix is reconstituted with 0.8 ml of Reconstitution Buffer; the Feeding Mix is reconstituted with 10.5 ml of Reconstitution Buffer; and the Energy Mix is reconstituted with 0.6 ml of Reconstitution Buffer. 0.5 ml of the Energy Mix was added to the Feeding Mix to obtain the Feeding Solution. 0.75 ml of Reaction Mix, 50 μ l of Energy Mix, and 10 μ g of the template DNA is added to the *E. coli* lysate.

[0338] Using the reaction device (Roche Biochem), 1 ml of the Reaction Solution is loaded into the reaction compartment. The reaction device is turned upside-down and 10 ml of the Feeding Solution is loaded into the feeding compartment. All lids are closed and the reaction device is loaded into the RTS500 instrument. The instrument is run at 30°C for 24 hours with a stir bar speed of 150 rpm. The pIVEX 2.3 MCS vector includes a nucleotide sequence that encodes six consecutive histidine amino acids on the C-terminal end of the target polypeptide for the purpose of protein purification. Target polypeptide is purified by contacting the contents of reaction device with resin modified with Ni²⁺ ions. Target polypeptide is eluted from the resin with a solution containing free Ni²⁺ ions.

Example 18

Cellular Production of Target Polypeptides

[0339] Nucleic acids are cloned into DNA plasmids having phage recombination sites and target polypeptides are expressed therefrom in a variety of host cells. Alpha phage genomic DNA contains short sequences known as attP sites, and *E. coli* genomic DNA contains unique, short sequences known as attB sites. These regions share homology, allowing for integration of phage DNA into *E. coli* via directional, site-specific recombination using the phage protein Int and the *E. coli* protein IHF. Integration produces two new att sites, L and R, which flank the inserted prophage DNA. Phage excision from *E. coli* genomic DNA can also be accomplished using these two proteins with the addition of a second phage protein, Xis. DNA vectors have been produced where the integration/excision process is modified to allow for the directional integration or excision of a target DNA fragment into a backbone vector in a rapid *in vitro* reaction (Gateway™ Technology (Invitrogen, Inc.)).

[0340] A first step is to transfer the nucleic acid insert into a shuttle vector that contains attL sites surrounding the negative selection gene, ccdB (*e.g.* pENTER vector, Invitrogen, Inc.). This transfer process is accomplished by digesting the nucleic acid from a DNA vector used for sequencing, and to ligate it into the multicloning site of the shuttle vector, which will place it between the two attL sites

while removing the negative selection gene *ccdB*. A second method is to amplify the nucleic acid by the polymerase chain reaction (PCR) with primers containing *attB* sites. The amplified fragment then is integrated into the shuttle vector using *Int* and *IHF*. A third method is to utilize a topoisomerase-mediated process, in which the nucleic acid is amplified via PCR using gene-specific primers with the 5' upstream primer containing an additional CACC sequence (*e.g.*, TOPO® expression kit (Invitrogen, Inc.)). In conjunction with Topoisomerase I, the PCR amplified fragment can be cloned into the shuttle vector via the *attL* sites in the correct orientation.

[0341] Once the nucleic acid is transferred into the shuttle vector, it can be cloned into an expression vector having *attR* sites. Several vectors containing *attR* sites for expression of target polypeptide as a native polypeptide, N-fusion polypeptide, and C-fusion polypeptides are commercially available (*e.g.*, pDEST (Invitrogen, Inc.)), and any vector can be converted into an expression vector for receiving a nucleic acid from the shuttle vector by introducing an insert having an *attR* site flanked by an antibiotic resistant gene for selection using the standard methods described above. Transfer of the nucleic acid from the shuttle vector is accomplished by directional recombination using *Int*, *IHF*, and *Xis* (LR clonase). Then the desired sequence can be transferred to an expression vector by carrying out a one hour incubation at room temperature with *Int*, *IHF*, and *Xis*, a ten minute incubation at 37°C with proteinase K, transforming bacteria and allowing expression for one hour, and then plating on selective media. Generally, 90% cloning efficiency is achieved by this method. Examples of expression vectors are pDEST 14 bacterial expression vector with *att7* promoter, pDEST 15 bacterial expression vector with a T7 promoter and a N-terminal GST tag, pDEST 17 bacterial vector with a T7 promoter and a N-terminal polyhistidine affinity tag, and pDEST 12.2 mammalian expression vector with a CMV promoter and neo resistance gene. These expression vectors or others like them are transformed or transfected into cells for expression of the target polypeptide or polypeptide variants. These expression vectors are often transfected, for example, into murine-transformed adipocyte cell line 3T3-L1, (ATCC), human embryonic kidney cell line 293, and rat cardiomyocyte cell line H9C2.

[0342] Modifications may be made to the foregoing without departing from the basic aspects of the invention. Although the invention has been described in substantial detail with reference to one or more specific embodiments, those of skill in the art will recognize that changes may be made to the embodiments specifically disclosed in this application, yet these modifications and improvements are within the scope and spirit of the invention, as set forth in the claims which follow. All publications or patent documents cited in this specification are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference.

[0343] Citation of the above publications or documents is not intended as an admission that any of the foregoing is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents. U.S. patents and other publications referenced herein are hereby incorporated by reference.

Nucleotide and Amino Acid Sequence Examples

[0344] Table B includes information pertaining to the incident polymorphic variant associated with osteoarthritis identified herein. Public information pertaining to the polymorphism and the genomic sequence that includes the polymorphism are indicated. The genomic sequences identified in Table B may be accessed at the http address

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=snp>, for example, by using the publicly available SNP reference number (e.g., rs910223). The chromosome position refers to the position of the SNP within NCBI's Genome Build 34, which may be accessed at the following http address: www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=. The "Contig Position" provided in Table B corresponds to a nucleotide position set forth in the contig sequence (see "Contig Accession No."), and designates the polymorphic site corresponding to the SNP reference number. The sequence containing the polymorphisms also may be referenced by the "Nucleotide Accession No." set forth in Table B. The "Sequence Identification" corresponds to cDNA sequence that encodes associated target polypeptides (e.g., PADI2). The position of the SNP within the cDNA sequence is provided in the "Sequence Position" column of Table B. If the SNP falls within an exon, the corresponding amino acid position (and amino acid change, if applicable) is provided as well. The amino acid found to be associated with OA is in bold. Also, the allelic variation at the polymorphic site and the allelic variant identified as associated with osteoarthritis is specified in Table B. All nucleotide and polypeptide sequences referenced and accessed by the parameters set forth in Table B are incorporated herein by reference. Genomic nucleotide sequences for *PADI2*, *APOB*, *IL1RL2*, *IL1RL1*, *WASPIP*, *ADAMTS2*, *BVES*, *TM7SF3*, *LOXL1*, *CNTNAP4 / CASPR4* and *APOL3* regions are set forth in SEQ ID NO: 1-13, respectively.

TABLE B

RS_ID	Chromosome	Chrom Position	Contig Accession No. [1]	Contig Position	Nucleotide Accession No. [2]	Sequence Position	Amino Acid Position	Locus	Locus ID	A [3]	Allelic Variability	OA Assoc. Allele
910223	1	16840936	Hs1_30840_34:10	284197	AL049569	24127		PADI2	11240	F	[A/G]	A
1367117	2	21238436	Hs2_22340_34:13	79834	NM_000384	coding-nonsynon	I98T	POB	338	F	[A/G]	G
1024791	2	102459310	Hs2_22327_34:13	4903934	NM_003854	intron		IL1RL2	8808	R	[G/A]	G
1041973	2	102576868	Hs2_22327_34:13	5021492	NM_003856	coding-nonsynon	E78A	IL1RL1	9173	R	[A/C]	C
1465621	2	175653334	Hs2_5560_34:14	25660207	NM_003387	mna-utr		WASPIP	7456	F	[T/A]	A
398829	5	178748273	Hs5_77500_34:3	1729878	NM_014244	coding-nonsynon	V245I	ADAMTS2	9509	R	[G/A]	G
1018810	6	105605179	Hs6_25897_34:13	9729038	NM_007073	intron		BVES	11149	F	[A/G]	A
1484086	12	27054610	Hs12_9871_34:16	19922317	NM_016551	intron		TM7SF3	51768	R	[T/C]	T
242392	14	54639492	Hs14_26604_34:1	36569492	NM_021255	intron		PEL12	57161	F	[C/T]	T
8818	15	71960095	Hs15_10351_34:1	45034596	NM_005576	mna-utr		LOXL1	4016	R	[G/C]	C
1395486	16	76223689	Hs16_24953_34:1	3155849	NM_033401	intron		CNTNAP4 / CASPR4	85445	F	[C/T]	T
512294	X	148992251	HsX_11883_34:11	1234340	NM_004224	UTR		GPR50	9248	F	[A/G]	G
132659	22	34831250	Hs22_11677_34:9	15897265	NM_014349	mna-utr		APOL3	80833	F	[C/T]	C

[1] Contig Accession Number which can be found in the NCBI Database:
http address: www.ncbi.nih.gov/entrez/query.fcgi

[2] Sequence Identification or Nucleotide Accession Number which can be found in the NCBI Database:
http address: www.ncbi.nih.gov/entrez/query.fcgi

[3] "A" column is the sequence orientation ("F" is forward, "R" is reverse).

[0345] Following are genomic nucleotide sequences for a *PADI2* region (SEQ ID NO: 1), a *APOB* region (SEQ ID NO: 2), a *IL1RL2* region (SEQ ID NO: 3), a *IL1RL1* region (SEQ ID NO: 4), a *WASPIP* region (SEQ ID NO: 5), a *ADAMTS2* region (SEQ ID NO: 6), a *BVES* region (SEQ ID NO: 7), a *TM7SF3* region (SEQ ID NO: 8), a *PELI2* region (SEQ ID NO: 9), a *LOXL1* region (SEQ ID NO: 10), a *CNTNAP4 / CASPR4* region (SEQ ID NO: 11), a *GPR50* region (SEQ ID NO: 12), and a *APOL3* region (SEQ ID NO: 13). The following nucleotide representations are used throughout: "A" or "a" is adenosine, adenine, or adenylic acid; "C" or "c" is cytidine, cytosine, or cytidylic acid; "G" or "g" is guanosine, guanine, or guanylic acid; "T" or "t" is thymidine, thymine, or thymidylic acid; and "I" or "i" is inosine, hypoxanthine, or inosinic acid. Exons are indicated in italicized lower case type, introns are depicted in normal text lower case type, and polymorphic sites are depicted in bold upper case type. SNPs are designated by the following convention: "R" represents A or G, "M" represents A or C; "W" represents A or T; "Y" represents C or T; "S" represents C or G; "K" represents G or T; "V" represents A, C or G; "H" represents A, C, or T; "D" represents A, G, or T; "B" represents C, G, or T; and "N" represents A, G, C, or T.

PADI2 genomic sequence (SEQ ID NO: 1)

>16 : PADI2

GGCTCAGAGGCACCGCAGAGCCTCCCGGGCCAGGGTCTGCACTGGTCCCA [A/G] CCACACACAGTAAGACACTGGAAAAACCAAC
TCAACAAATGTGTCCAGGT

APOB genomic sequence (SEQ ID NO: 2)

>2:21188451-21288350

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61     ccacatccct gaccaaaaat tcctgcacagg tggcagccgg cctcttagca acgccaccag
121    gagcctggag ttatccaggg gccacgggtg ttcccttagg ccaggtacag ggcggagttg
181    ggagacctcc tgctgggagg aaggagccca tgaaggcagc gctcagcctc cagagccRcc
241    ctgtgacagg tcaggggaca gccttggatg ggccatgaga gcccacctcc tgtRYcccct
301    taaggtgggc ccccggtttt ccaccagact gggagactca caggaKgca gtttgtttgc
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421    caagactccc ttctcacctg ctcacccagg cctctcaca ctaccttgtt ccaagtggcc
481    tgatattctg cctgctaggc acacatagtc tgtacccttt taaggtacaa gtggggaaga
541    aggacacttt ctgtcacgtc cattaccaca aattcctgac aggtggcagc tgggctctgt
601    gggaaaagga ccaacatgct cagttgagct tagcacctcc tgaggcctcc ttagcaaggc
661    tggagcctgg cctgtggagg agacaggtgt cccagctgtg gcccagaagt gtgcaaaggt
721    tgaggggtgag aaggtggaaa gactatgggg ttgggcaagg aggtataatc tccgcttggg
781    gcatggctgg aggagagcag gtaatggagg ggtggggagg gctcccagga aggagggcct
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1321   ctgctcgtaa gcaagccatc acagaaataa aagctgacag aaagcgtgtg ttctgtccag
1381   gaagagaaag tttctgcaag aaacaagata gtgcagagag ctggMctgtg ctggaccagt
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1921   atcctgtcct cacactggag tgagagtggg cagagacact cattcccata ctgaggaaag
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2161   aggagcctgc actggaggcg agagtggagc ctggctcagg gactgactct ccagggaat
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CASPR4 genomic sequence (SEQ ID NO: 11)

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GPR50 genomic sequence (SEQ ID NO: 12)

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APOL3 genomic sequence (SEQ ID NO: 13)

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92461  aatggggccag gattatgatc taag.tttttca aatgaggaaa ctgaggcaag gggcgaggaa
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[0346] Following are cDNA sequences for *PADI2* (SEQ ID NO: 14), *APOB* (SEQ ID NO: 15), *IL1RL2* (SEQ ID NO: 16), *IL1RL1* (SEQ ID NO: 17-19), *WASPIP* (SEQ ID NO: 20), *ADAMTS2* (SEQ ID NO: 21-22), *BVES* (SEQ ID NO: 23-24), *TM7SF3* (SEQ ID NO: 25), *PELI2* (SEQ ID NO: 26), *LOXL1* (SEQ ID NO: 27), *CASPR4 (aka CNTNAP4)* (SEQ ID NO: 28-29), *GPR50* (SEQ ID NO: 30), and *APOL3* (SEQ ID NO: 31-36).

PADI2 cDNA sequence (SEQ ID NO: 14)

NM_007365 Homo sapiens peptidyl arginine deiminase, type II (*PADI2*), mRNA

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2341  aacctgtg

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APOB cDNA sequence (SEQ ID NO: 15)

NM_000384 Homo sapiens apolipoprotein B (including Ag(x) antigen) (APOB), mRNA

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IL1RL2 cDNA sequence (SEQ ID NO: 16)

NM_003854 Homo sapiens interleukin 1 receptor-like 2 (IL1RL2), mRNA.

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1 cccgcccacg gtggcgggga aatacctaggt catggaagtg gcatgacagg gc t cgtgtcc
61 ctgtcatatt ttccactctc cacgaggtcc tgcgcgcttc aatcctgcag gc agcccggt
121 ttgggggatgt ggtccttgtc gctctgcggg ttgtccatcg cccttccact gt ctgtcaca
181 gcagatggat gcaaggacat ttttatgaaa aatgagatac tttcagcaag cc agcctttt
241 gctttttaatt gtacattccc tcccataaca tctggggaaag tcagtgtaac at ggtataaa
301 aattctagca aaatcccagt gtccaaaatc atacagtcta gaattcacca gg acgagact
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421 ggtagagaca gctgtcatag aatacatgta aacctaacgt tttttgaaaa ac attgggtgt
481 gacacttcca taggtggttt accaaattta tcagatgagt acaagcaaat at tacatctt
541 ggaaaagatg atagtctcac atgtcatctg cacttcccga agagttgtgt tt tgggtcca
601 ataaagtggg ataaggactg taacgagatt aaaggggagc ggttcactgt tt tggaaacc
661 aggccttttg tgagcaatgt ctcggcagag gacagaggga actacgcgtg tc aagccata
721 ctgacacact cagggaagca gtacgaggtt ttaaattggca tcactgtgag ca ttacagaa
781 agagctggat atggaggaag tgtccctaaa atcatttatc caaaaaatca tt caattgaa
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901 aatctacgat gctggagagt caataacact ttgggtggatg attactatga tg aatccaaa
961 cgaatcagag aaggggtgga aacctatgtc tcttttcggg aacataatth gt acacagta
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1141 ataggagggc ttatcgccct ggtggctgtg gctgtgtctg ttgtgtacat at acaacatt
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1261 gatgggaagc tgtatgacgc ctatgtctta tacoccaagc ccacaagga aa gccagagg
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1561 gacgggatga aggttattct cattgagtag gagaaaaatc aggactacac ag tcatgcca
1621 gagtcaatc agtacatcaa acagaagcat ggtgccatcc ggtggcatgg gg acttcaag
1681 gagcagtcac agtgtatgaa gaccaagttt tgggaagacag tgagatacca ca tggcggcc
1741 agaaggtgtc ggcgctttcc tccggtccag ctgctgcagc acacaccttg ct accgcacc
1801 gcagggccag aactaggctc aagaagaaag aagtgtactc tcacgactgg ct aagacttg
1861 ctggactgac acctatggct tgaagatgac ttgttttgc ccatgtctcc tc atttctac
1921 acctattttc tgctgcagga tgaggctagg gttagcattc taga

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IL1RL1 cDNA sequence 1 (SEQ ID NO: 17)

NM_016232 Homo sapiens interleukin 1 receptor-like 1 (IL1RL1), transcript variant 1, mRNA

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1 aaagagagggc tggctgttgt atttagtaaa gctataaagc tgtaagagaa attggctttc
61 tgagtgtgtga aactgtgggc agaaagtgtga ggaagaaaga actcaagtac aaccaatga
121 gggttgagata taggctactc ttcccaactc agtcttgaag agtatcacca actgcctcat
181 gtgtggtgac cttcactgtc gtatgccagt gactcatctg gagtaatctc aacaacgagt
241 taccaatact tgctcttgat tgataaacag aatgggggtt tggatcttag caattctcac
301 aattctcatg tattccacag cagcaaagtt tagtaaacaa tcatgggggc tggaaaatga
361 ggctttaatt gtaagatgtc ctgacaagg aaaacctagt tacaccgtgg attggtatta
421 ctcacaaaca aacaaaagta ttcccactca ggaagaaat cgtgtgtttg cctcaggcca
481 acttctgaag tttctaccag ctgcagttgc tgattctggg atttatacct gtattgtcag
541 aagtcccaca ttcaatagga ctggatatgc gaatgtcacc atatatataa aacaatcaga
601 ttgcaatggt ccagattatt tgatgtattc aacagtatct ggatcagaaa aaaattccaa
661 aatttattgt cctaccattg acctctacaa ctggacagca cctcttgagt ggtttaagaa
721 ttgtcagggt cttcaaggat caaggtagac ggcgcacaag tcatttttgg tcattgataa
781 tgtgatgact gaggacgcag gtgattacac ctgtaaattt atacacaatg aaaatggagc
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901 gtttccagta atcggagccc ctgcacaaaa tgaaataaag gaagtggaaa ttggaaaaaa
961 cgcaaaccta acttgctctg cttgttttgg aaaaggcact cagtcttgg ctgccgtcct
1021 gtggcagctt aatggaacaa aaattacaga ctttggtgaa ccaagaattc aacaagagga
1081 agggcaaat caaagtttca gcaatgggct ggcttgtcta gacatggttt taagaatagc
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1201 cttgagaagg cacaccgtaa gactaagtag gaaaaatcca attgatcatc atagcatcta
1261 ctgcataatt gcagtatgta gtgtattttt aatgtccttg ttatcatcct
1321 aaaaatgttc tggattgagg ccactctgct ctggagagac atagctaaac cttacaagac
1381 taggaatgat ggaaagctct atgatgctta tgttgtctac ccacggaact acaaatccag
1441 tacagatggg gccagtcgtg tagagcactt tgttcaccag attctgcctg atgttcttga
1501 aaataaatgt ggctatacct tatgcattta tgggagagat atgtcacctg gagaagatgt
1561 agtcactgca gtggaaccca acatacgaaa gagcaggcgg cacattttca tcctgacccc
1621 tcagatcact cacaataagg agtttgctta cgagcaggag gttgccctgc actgtgccct
1681 catccagaac gacgccaaag tgatacttat tgagatggag gctctgagcg agctggacat
1741 gctgcagggt gaggcgcttc aggactccct ccagcatctt atgaaagtac aggggaccat
1801 caagtggagg gaggaccaca ttgccataaa aaggtccttg aattctaaat tctggaagca
1861 cgtgaggtag caaatgcctg tgccaagcaa aattcccaga aaggcctcta gtttgactcc
1921 cttggctgcc cagaagcaat agtgctgct gtgatgtgca aaggcatctg agtttgaagc
1981 tttcctgact tctcctagct ggcttatgcc cctgcactga agtgtaggga gcaggaatat
2041 taaagggatt caggcctc

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IL1RL1 cDNA sequence 2 (SEQ ID NO: 18)

NM_003856 Homo sapiens interleukin 1 receptor-like 1 (IL1RL1), transcript variant 2, mRNA

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1 gaggagggac ctacaaagac tggaaactat tcttagctcc gtcactgact ccaagttcat
61 cccctctgtc tttcagtttg gttgagatat aggtactctc tcccaactca gtcttgaaga
121 gtatcaccaa ctgcctcatg tgtggtgacc ttcactgtcg tatgccagtg actcatctgg
181 agtaatctca acaacgagtt accaataact gctcttgatt gataaacaga atggggtttt
241 ggatcttagc aattctcaca attctcatgt attccacagc agcaaagttt agtaaacaa
301 catggggcct ggaaaatgag gctttaattg taagatgtcc tagacaagga aaacctagtt
361 acaccgtgga ttggtattac tcacaaacaa acaaaagtat tcccactcag gaaagaaatc
421 gtgtgtttgc ctcaggccaa cttctgaagt ttctaccagc tgcaattgct gattctggta
481 tttatacctg tattgtcaga agtcccacat tcaataggac tggatatgcg aatgtcacca
541 tatataaaaa acaatcagat tgcaatgttc cagattattt gatgtattca acagtatctg
601 gatcagaaaa aaattccaaa atttattgtc ctaccattga cctctacaac tggacagcac
661 ctcttgagtg gtttaagaat tgtcaggctc ttcaaggatc aaggtagagg gcgcacaagt
721 catttttggg cattgataat gtgatgactg aggacgcagg tgattacacc tgtaaaattt
781 tacacaatga aaatggagcc aattatagtg tgacggcgac caggtccttc acggtcaagg
841 attgagcaagg ctttctctgt tttccagtaa tcggagcccc tgcaaaaaat gaaataaagg
901 aagtggaaat tggaaaaaac gcaaacctaa cttgctctgc ttgttttggg aaaggcactc

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961 agttcttggc tggcgtcctg tggcagctta atggaacaaa aattacagac tttggtgaac
1021 caagaattca acaagaggaa gggcaaaatc aaagtttcag caatgggctg gcttgtctag
1081 acatgggtttt aagaatagct gacgtgaagg aagaggattt attgctgcag tacgactgtc
1141 tggccctgaa tttgcatggc ttgagaaggg acaccgtaag actaagtagg aaaaatccaa
1201 gtaaggagtg tttctgagac tttgatcacc tgaactttct ctagcaagtg taagcagaat
1261 ggagtgtggg tccaagagat ccatcaagac aatgggaatg gcctgtgcca taaaatgtgc
1321 ttctcttctt cgggatgttg tttgctgtct gatctttgta gactgttcct gtttgcctgg
1381 agcttctctg ctgcttaaat tggtcgtcct cccccactcc ctctatcgt tggtttgtct
1441 agaacactca gctgcttctt tggtcacctt tggtttctaa ctttatgaac tccctctgtg
1501 tcaactgtatg tgaaggaaaa tgcaccaaca accgtaaact gaacgtgttc ttttgtgctc
1561 ttttataact tgcattacat gttgtaagca tgggtccgtt tatacctttt tctggtcata
1621 atgaacactc attttgttag cgagggtggg aaagtgaaca aaaaggggaa gtatcaaact
1681 actgccattt cagtgaagaa atcctaggtg ctactttata ataagacatt tgttaggcca
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2401 gggcagggac atcatctctt ccatctttgg gtccttagtg caatacctgg cagctagcca
2461 gtgctcagct aaatatttgt tgactgaata aatgaatgca caacaaaaaa aaaaaaaaaa
2521 aaaaaaaaaa aaaaaaaaaa aa

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IL1RL1 cDNA sequence 3 (SEQ ID NO: 19)

NM_173459 Homo sapiens interleukin 1 receptor-like 1 (IL1RL1), transcript variant 3, mRNA

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1 gaggagggac ctacaaagac tggaaactat tottagctcc gtcactgact ccaagttcat
61 cccctctgtc tttcagtttg gttgagatat aggctactct tcccaactca gtcttgaaga
121 gtatcaccaa ctgcctcatg tgtggtgacc ttcactgtcg tatgccagtg actcatctgg
181 agtaatctca acaacgagtt accaatactt gctcttgatt gataaacaga atggggtttt
241 ggatctagct aattctcaca attctcatgt attccacagc agcaaagttt agtaaacaa
301 catggggcct ggaaaatgag gctttaattg taagatgtcc tagacaagga aaacctagtt
361 acaccgtgga ttggtattac tcacaaacaa acaaaagtat tcccactcag gaaagaatc
421 gtgtgttttg ctcaggccaa cttctgaagt ttctaccagc tgcagttgct gattctggta
481 tttataacctg tattgtcaga agtcccacat tcaataggac tggatatgcy aatgtcacca
541 tatataaaaa acaatcagat tgcaatgttc cagattattt gatgtattca acagtatctg
601 gatcagaaaa aaattccaaa atttattgtc ctaccattga cctctacaac tggacagcac
661 ctcttgagtg gtttaagaat tgtcaggctc ttcaaggatc aaggtacagg gcgcacaagt
721 catttttggg cattgataat gtgatgactg aggacgcagg tgattacacc tgtaaattta
781 tacacaatga aaatggagcc aattatagtg tgacggcgac caggtccttc acggtcaagg
841 tttggtgtca gagtttctgc aaattaaaaa agagcttaat cttagtaaat actcattgga
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1021 cttttctctg tttccagtaa tggagcccc tgcacaaaat gaaataaagg aagtggaaat
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1261 aagaatagct gacgtgaagg aagaggattt attgctgcag tacgactgtc tggccctgaa
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2581 atcatctctt ccactctttg gtccttagtg caatacctgg cagctagcca gtgctcagct
2641 aaatatttgt tactgaata aatgaatgca caacaaaaaa aaaaaaaaaa aaaaaaaaaa
2701 aaaaaaaaaa aa

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WASPIP cDNA sequence 1 (SEQ ID NO: 20)

NM_003387 Homo sapiens Wiskott-Aldrich syndrome protein interacting protein (WASPIP), mRNA

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1 tagaagacag caggggaact cgagaagttg gttgttttca gcagattaaa acaatacaga
61 tttatcagca agactgttga acgcataact gcccaagatg cctgtccctc cccctccagc
121 acccccgccg cccccgacgt ttgcactggc caatacagag aagcctacct tgaataagac
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2521 tgaccttcga ttttcctccc ttaacttccc tcttccctta atatctgtat acaagtgttg
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3961 aaaactatga ataagttctg ttgtaaaatc ttaaactatg gaaaattaca aaaatgaatt
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4081 attcaacatg taatacagta ttttaacatt cacctcttat tttatattga aatgtattac
4141 agtattaaaa ctcatgttc agtattttat tcatatgca ttttatttag taaaagccag
4201 gagaaatggt taatccaatg ttgccttact ttgtgattta aaagaaatca actttttttt
4261 atgtctaagt agtagattat ttgcataatt gtaaaaactg ttaggtcttt atatttttaa
4321 gtgtaatacc agttttgtta ttttagtagc agaaatggga tgattgttaa agttccccaa
4381 aaatgttggc atgaaattaa ttttccctc cttatagtca aggaccgtag aggaagaaaa
4441 actttttttt cataccatgc actatgtaaa cacacacatt ttgctatctg tgtcatcagg
4501 atagtgttaag ttgtagggtg gagactaccc tagacatctg catctttgta agttagccag
4561 acaataaaga aaagcagaat gaaaaaaaaa aaaaaaaaaa aaaaa

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ADAMTS2 cDNA sequence 1 (SEQ ID NO: 21)

NM_014244 Homo sapiens a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 2 (ADAMTS2), transcript variant 1, mRNA

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1 atggatccgc cggcgggagc cgctcgccgc ctgctctgcc ccgcgctgct gctgctgctg
61 ctgctgctgc cgcgcgcgct cctgccgcgc ccgcgcgcgc ccgcgaacgc caggctcgcc
121 gccgcgcgcg acccccaggg cgggcccctg gggcacggag cggagcgcat cctggcggtg
181 cccgtgcgca ctgacgcca gggcgcttg gtgtccacg ttggtgtcggc agctacgtcc
241 agagcagggg tacgagcccg cagggcgcgc ccggtccgga ccccgagctt ccccgaggc
301 aacgaggagg agcctggcag tcacctcttc tacaatgtca cggctcttgg ccgagacctg
361 cacctgcggc tgcggcccaa cgccgcctc gtggcgcccg gggccactat ggagtggcag
421 ggcgagaagg gcaccacccg cgtggagccc ctgctcggga gctgtctcta cgtcggagac
481 gtggccggcc tagccgaagc ctctctgtg gcgtcagca actgcgatgg gctggctggt
541 ctgatccgga tggaggagga ggagttcttc atcgaacctt tggagaaggg gctggcgcg
601 caggaggctg agcaaggccg tgtgcatgtg gtgtatcgcc ggccaccac gtcccctct
661 ctgggggggc cacaggccct ggacacaggg gcctccctgg acagcctgga cagcctcagc
721 cgcgcctcgg gcgtcctaga ggagcacgcc aacagctcga ggcggagggc acgcaggcat
781 gctgcagacg atgactacaa catcgagggtc ctgctgggag tggatgactc tgtggtgcag
841 ttccacggga aggagcacgt acagaagtac ctgctgacac tcatgaacat tgtcaatgaa
901 atctaccatg acgagtcctt gggtagccac atcaacgtgg tcttggtcgc gatcatcctc
961 ctgagctatg gaaagtccat gagcctcatc gagatcggga acccctctca gagcctggag
1021 aatgtctgcc gctgggccta cctccagcag aagccagaca cgggccacga tgaataccac
1081 gatcacgcca tcttctcac acggcaggac tttgggcctt ccggcatgca aggctatgct
1141 cctgtcaccg gcattgtgcca tccggtccgc agctgcaccc tgaaccatga ggacggcttc
1201 tctcagcgt ttgtgtgggc ccatgagact ggccacgtgc tgggcatgga gcacgacggg
1261 cagggaacc gctgtggcga cgaggtgcgg ctgggcagca tcatggcgcc cctggtgcag

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1321 gccgccttcc accgcttcca ctggtcccgc tgcagccagc aggagctgag ccgctacctg
1381 cactcctatg actgcctgct ggatgaaccc ttccgccacg actggccggc gctgccccag
1441 ctcccgggac tgcactactc catgaacgag caatgccgct ttgacttcgg cctgggctac
1501 atgatgtgca cggcggttccg gacctttgac ccctgcaagc agctgtggtg cagccatcct
1561 gacaaccctt actttttgcaa gaccaagaag gggcccccct tggacgggac tatgtgtgca
1621 cctggcaagc attgttttaa aggacactgc atctggctga cacctgacat cctcaaaccg
1681 gacggcagct gggggcgcttg gagtccgttt ggctcctgct cactgacctg tggcacgggc
1741 gtgaagtcca ggaacccgca gtgtgacaac ccacaccggg ccaacggggg ccgcacctgc
1801 tcgggccttg cctacgactt ccagctctgc agccgccagg actgccccga ctccctggct
1861 gacttccgcy aggagcagtg ccgccagtg gacctgtact tcgagcacgg cgacgccag
1921 caccactggc tgcacccacga gcaccgggat gccaaaggaga gatgccacct gtactgcyag
1981 tccagggaga ccggggaggt ggtgtccatg aagcgcatgg tgcattgatg gacgcgctgc
2041 tcctacaagg acgccttcag cctctgtgtg cgcggggact gcaggaaggt gggctgtgac
2101 ggtgtgatcg gctccagcaa gcaggaagac aagtgtggcg tgtgcggagg ggacaacagc
2161 cactgcaaag tgggtcaaggg caggttcaca cggtcaccca agaagcatgg ttacatcaag
2221 atgtttgaga tccctgcagg agccagacac ctgctcattc aggaggtaga cgcaccacgc
2281 caccatctgg ccgtcaagaa cctggagaca ggcaagttca tcttaaatga agagaatgac
2341 gtggatgcca gttccaaaaa cttcattgac atgggcgtgg agtgggagta cagagacgag
2401 gacggccggg agacgctgca gaccatgggc cccctccacg gcaccatcac cgttctggct
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2521 ctgaatgtcg atgacaacaa cgtcctggaa gaggactctg tgggtctacg gtgggcccctg
2581 aagaagtggc ctccgtgctc caagccctgt ggccggagggt cccagttcac caagtatggc
2641 tgccgcggga ggtgggacca caagatggta caccgtggct tctgtgccgc cctctcgaag
2701 cccaaagcca tccgcagagc gtgcaaccca caggaaatgt cccagccagt gtgggtcaca
2761 ggcaaatggg agccatgtag ccagacctgt gggcggacag gcatgcaggt gcgctccgtg
2821 cgctgcattc agccgctaca cgacaacacc acccgctccg tgcacgcaa gcaactgcaat
2881 gacgcccggc ccgagagccg ccgggcctgc agccgcgagc tctgccctgg tcgttggcga
2941 gccgggccc tggcccagtg ctcaagtaac tgtggcaacg gcacccagga ggggccagtg
3001 cccgtccgca ccgcgagcga cagcttcggc atctgcaggg aggagcgtcc tgagacagcg
3061 aggacctgca ggcttggccc ctgtccccga aacatctcag atccctccaa gaagagctac
3121 gtagttcagt ggctgtcccg cccggacccc gactcgcca tccggaagat ctcgtaaaag
3181 ggccactgcc aaggcgacaa gtcaatatcc tgtaggatgg aagtcttgtc ccgctattgc
3241 tccatcccag gctacaacaa gctgtcctgc aagtcctgta acctgtacaa caacctcacc
3301 aacgtggagg gcagagtaga gccaccgccc ggaagcaca acgacattga cgtgttcatg
3361 cctaccctcc cagtgcacac tgtagccatg gaggtgcggc catcaccaag cccccctg
3421 gaggtccctc tcaatgcctc cagcaccaat gccacagagg atcacccaga aaccaatgcc
3481 gtagatgaac cctacaaaat ccatggcctg gaagatgaag tccagccacc caacctaatc
3541 cctcgacgac cgagccccta tgaaaagacc agaaaccaa gaatccaaga gctcattgat
3601 gagatgcgga agaaagagat gtcgggaaag ttctaa

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ADAMTS2 cDNA sequence 2 (SEQ ID NO: 22)

NM_021599 Homo sapiens a disintegrin-like and metalloprotease (reprolysin type) with thrombospondin type 1 motif, 2 (ADAMTS2), transcript variant 2, mRNA

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1 atggatccgc cggcgggagc cgctcgccgc ctgctctgcc ccgcgctgct gctgctgctg
61 ctgctgctgc cgccgcgcgt cctgccgcgc ccgcgcgcgc ccgcgaacgc caggctcgcc
121 gccgcgcgcg acccccacgg cgggccctct gggcacggag cggagcgcat cctggcggtg
181 cccgtgcgca ctgacgccc aaggccgctt gtgtcccacg tgggtgtcggc agctacgtcc
241 agagcagggg tacgagcccg cagggcgcgc ccggtccgga ccccgagctt ccccgagggc
301 aacgaggagg agcctggcag tcacctcttc tacaatgtca cggctcttgg ccgagacctg
361 cactgcggc tgccggccaa cgccgcgcct gtggcgcccg gggccactat ggagtggcag
421 gccgagaagg gcacaccccg cgtggagccc ctgctcggga gctgtctcta cgtcggagac
481 gtggccggcc tagccgaagc ctctctgtg gcgctcagca actgcgatgg gctggctggt
541 ctgatccgga tggaggagga ggagttcttc atcgaaccct tggagaaggg gctggcgggc
601 caggaggctg agcaaggccg ggacacaggg gcctccctgg acagcctgga cagcctcagc
661 ctccgggggg cacagccctg ggacacaggg gcctccctgg acagcctgga cagcctcagc
721 cgcgcctgg gcgtctaga ggagcacgcc aacagctcga ggcggagggc acgcaggcat
781 gctgcagacg atgactacaa catcgagggt ctgctggggc tggatgactc tgtgggtgcag
841 ttccacggga aggagcacgt acagaagtac ctgctgacac tcatgaacat tgtcaatgaa
901 atctaccatg acgagtcctt ggggtgccac atcaacgtgg tccctgggtcg gatcatcctc
961 ctgagctatg gaaagtcctt gagcctcatg gagatcggga acccctctca gagcctggag
1021 aatgtctgcc gctgggccta cctccagcag aagccagaca cgggccacga tgaataccac

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1081 gatcacgcca tcttcctcac acggcaggac tttgggcctt cgggcatgca aggcctatgct
1141 cctgtcaccg gcatgtgcca tccgggtccg agctgcaccc tgaaccatga ggaagggttc
1201 tcctcagcgt ttgtggtggc ccatgagact ggccacgtgc tgggcatgga gcaagacggg
1261 cagggcaacc gctgtggcga cgagggtgcg ctgggcagca tcatggcgcc cctggtgcag
1321 gccgccttcc accgcttcca ctgggtccgc tgcagccagc aggagctgag ccgctacctg
1381 cactcctatg actgcctgct ggatgacccc ttgcccacg actggccggc gctgccccag
1441 ctcccgggac tgcactactc catgaacgag caatgccgct ttgacttcgg cctgggctac
1501 atgatgtgca cggcggttccg gacctttgac ccctgcaagc agctgtggtg cagccatcct
1561 gacaacccct acttttgcaa gaccaagaag gggccccct tggacgggac tatgtgtgca
1621 cctggcaagt tcaggccggg cgcggtggct catgcctgtt atcccagcac tttgggaggc
1681 caaggtaggt ggatcgctg a

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BVES cDNA sequence 1 (SEQ ID NO: 23)

NM_007073 Homo sapiens blood vessel epicardial substance (BVES), transcript variant A, mRNA

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1 tcaggcagcc ccagcgtccc cggggccctcg gccccaccga gtgccggctc ccgcgctctg
61 cggcggcaag ccccttgga ttttcaaat gaattataca gaggccagcc catgtagaga
121 atcaactgcc ataggtttta cactgagact agaaagtatc atacctgtgc cttccaataa
181 gaccacttgt gaaaactgga gagagataca tcatctggtt tttcatgtag caaatatttg
241 ttttgcagtt ggggttggtta ttccaactac tcttcacctt catatgatat ttcttagggg
301 aatgttaact ctaggatgta ccttttatat cgtctgggac actctctacc gatgtgcctt
361 ggatataatg atctggaact ctgtgttctt ggggtgtcaac attttgcac tgtcgtatct
421 ttatatacag aagagaccgg taaagattga aaaggaaact agtggcatgt accggcgatt
481 gtttgaacca ctccgtgtgc ctccagatgt gttcagaaga ctaactggac agttttgcat
541 gatccaaacc ttgaaaaagg gccaaactta tgctgcagag gataaaacct cagttagatga
601 cgtctgagat attctcttga agggaaaaat gaagggtctc tatcgaggac attttctgca
661 taacatttac cctgtgacct ttatagattc tctgaattt agatcaactc agatgcacaa
721 aggtgaaaaa ttccaggtca ccattattgc agatgataac tgcagatttt tatgctggtc
781 aagagaaaga ttaacatact ttctggaatc agaacccttc ttgtatgaaa tctttaggta
841 tcttatttga aaagacatca caaataagct ctactcattg aatgatccca ccttaaataa
901 taaaaaagcc aaaaagctgg aacatcagct cagcctctgc acacagatct ccatgttgga
961 aatgaggaac agtatagcca gctccagtga cagtgaagac ggcttgacac agtttcttctg
1021 ggttacctcc agcatgtcct ctcttcattg gtcaccccca caccagcgag cctctgccaa
1081 gatgaaaccg atagaagaag gagcagaaga tgatgatgac gtttttgaac cggcatctcc
1141 aaatacattg aaagtccatc agctgccttg atcagagaga gaattcaggt taaccaagacg
1201 gaagggtgtc tgaagagatc ctgaaaaata ccagcacttt ttcattggctt ttagggttatt
1261 ctgctttagt gcatccagac tgggtggagtc ggagggagga agtgaggaa ggtcaaggat
1321 ggaagagttc tttcacctac cctttttatt agtcagcttt taaagtaatt gttttactga
1381 gcctcttgac tatgccttgt tctcttttga gatatatatt ttcacagtct tttctagata
1441 tattattgtt ttaacttaac aaatcttagc aatctctcaa tgccttttca ctctattttt
1501 tccaagttat gattcttttt cctcacagtc ttttttgttc catagcaatg aggttgtcca
1561 tttgataatt ttaacaaaca atgtaagttt aaaattgagg ctaaggtaac atgaaaaagc
1621 agggaatctc aaactttat

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BVES cDNA sequence 2 (SEQ ID NO: 24)

NM_147147 Homo sapiens blood vessel epicardial substance (BVES), transcript variant B, mRNA

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1 agagcgccga tggctgggga cccgaggtcc ggcgccacca cccgcaacct ccttccccga
61 gcctttggga acgggttggt ggccagacaa gtcccagaaa ctgcctgctt tgaagcatga
121 ataagtgcga aaagactctt agcaatgaat tttcaaatg aattatacag agtccagccc
181 attgagagaa tcaactgcca taggttttac acctgagtta gaaagtatca taactgtgcc
241 ttccaataag accacttgtg aaaactggag agagatacat catctgggtt tcatgtagc
301 aaatatttgt tttgcagttg ggttggttat tccaactact cttcaccttc atatgatatt
361 tcttagggga atgttaactc taggatgtac cctttatatc gtctgggcca ctctctaccg
421 atgtgccttg gatataatga tctggaactc tgtgttcttg ggtgtcaaca ttgtgcatct
481 gtcgtatctt ttatacaaga agagaccggg aaagattgaa aaggaactca gtggcatgta
541 ccggcgattg tttgaaccac tccgtgtgcc tccagatttg ttcagaagac taactggaca

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601 gttttgcatg atccaaacct tgaaaaaggg ccaaacttat gctgcagagg ataaaaacctc
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721 ttttctgcat aacattttacc cctgtgcctt tatagattct cctgaattta gatcaactca
781 gatgcacaaa ggtgaaaaat tccaggtcac cattattgca gatgataact gcagatTTTT
841 atgctgggtca agagaaagat taacatactt tctggaatca gaacctttct tgtatgaaat
901 ctttaggtat ctatttgga aagacatcac aaataagctc tactcattga atgatccac
961 cttaaattgat aaaaaagcca aaaagctgga acatcagctc agcctctgca cacagatctc
1021 catgttgga atgaggaaca gtatagccag ctccagtgac agtgacgacg gcttgacca
1081 gtttcttcgg ggtacctcca gcatgtcctc tcttcattgt tcatccccc accagcgagc
1141 ctctgccaag atgaaaccga tagaagaagg agcagaagat gatgatgacg tttttgaacc
1201 ggcattctcca aatacattga aagtccatca gctgccttga tcagagagag aattcaggtt
1261 accaagacgg aaggtgtctt gaagagatcc tgaaaaatac cagcactttt tcatggcttt
1321 taggttattc tgcttttagt catccagact ggtggagtcg gagggaggaa gtgaggaaag
1381 tgcaaggatg gaagagttct ttcacttacc ctttttatta gtacgctttt aaagtaattg
1441 ttttactgag cttctgact atgccttgtt ctcttttgag atatatattt tcacagtcaa
1501 aaaaaaaaaa aaaa

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TM7SF3 cDNA sequence 2 (SEQ ID NO: 25)

NM_016551 Homo sapiens transmembrane 7 superfamily member 3 (TM7SF3), mRNA

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1 ccagccctgg cgtgggcccc gcccgcccc ggcagcaatg gggttcctgc agctgctggt
61 cgtagcgggt ctggcatccg aacaccgggt ggctgggtgca gccgaggtct tcgggaattc
121 cagcgagggt cttattgaat tttctgtggg gaaatttaga tacttcgagc tcaataggcc
181 ctttccagag gaagctatTT tgcatgata ttcaagcaat gtgacttttc ttattttcca
241 aatacactca cagtatcaga atacaactgt ttctttttct ccgactctcc tttccaattc
301 ctcggaacaa ggcactgcca gtggactggt tttcatcctt agaccagagc agagtacatg
361 cacttggtac ttggggactt caggcataca gcctgtccag aatatggcta tcctactctc
421 ctactcagaa agagatcctg tccctggagg ctgtaatttg gagttcgatt tagatattga
481 tcccaacatt tacttggagt ataattttct tgaacgact atcaagtttg cccagcaaaa
541 cctaggctat gcgagaggcg tagatcccc accatgtgac gctgggacag accagagctc
601 caggtggagg ttgcagtatg atgtctatca gtattttctg cctgagaatg acctcactga
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721 tctcaagggt gttaccctaa cagctaata taagacaagt gtttcttctt cctcctctcc
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901 cctaggaaga gtgtcttcca aagtgttctt cactcttttt gccctgcttg gtttcttcat
961 ttgtttcttt ggacacagat tctggaaaac agaattattc ttcatagggt ttatcatcat
1021 gggattcttc ttttatatac tgattacaag actgacacct atcaagtatg atgtgaatct
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1141 atttggaatc cttctgactt gcatgctctg tgttggaacta gtgctggggt tcctcatctc
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1261 ctgggtcact ttctcttgca tagctatcct cattccagta gttttcatgg gctgcctaag
1321 aatactgaac atactgactt gtggagtcac ttggtcctat tcggtggttt tagccattga
1381 cagttacttg tccacaagcc tttcctacat cactttgaac gtactcaaga gagcgctcaa
1441 caaggatttc cacagagctt tcacaaatgt gccttttcaa actaatgact tcattatcct
1501 ggcagtatgg ggcattgctg ctgtaagtgg aattacgtta cagattcgaa gagagagagg
1561 acgaccgttc ttccctcccc acccatacaa gttatggaag caagagagag agcgccgagt
1621 gacaaacatt ctggacccta gctaccacat tcttccattg agagagaggc tctatggccg
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1741 gcttctgtag atgcccaggg gcttggtcag tgtgcctcag cttggaggtt catgcttgga
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1861 gcataatatt atggtgccct tattgatata tggtaagggt gtactagggg attagatga
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1981 caaatacttg agaaattacc ttttggttta caaatctatg atcaacttat tccattaaat
2041 agatacatTA aaaaaattaa aaactgcaaa aaaaaaaaaa aaactggtgt ttctttttat
2101 aacccttgga aacaagtctc tcacctgagc ctgtctaaac tttcggaggg agtttattat
2161 tgagtcttta tctgtgacag tatttggaag tttagggtat tgatacttag gcctttgaat
2221 tttgaataac aaaaagagaa gcaagccaga catggtggct cacacctgta atcccaatac
2281 tgggaaggcca aggtgggagt atcgcttgag ccagagggtt tgagaccgac atgggcaaca
2341 tgacaagacc ccatctctac aaaaaaattt aaaaaattag ccaggcatgg tggcacatgc
2401 ctactcccag ctcccaagga gactgagatg ggaggatccc tggagccctg aagattgagg

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2461 ctacagttag ccttgattgt gtcactgcac tccagcttgg gtgacagaga ccctgtctcg
 2521 agaaatt

PELI2 cDNA sequence 2 (SEQ ID NO: 26)

NM_021255 Homo sapiens pellino homolog 2 (Drosophila) (PELI2), mRNA

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1  cagccacgac ggagcagcag cgggactggc cgccccgcgc ccccttcgcc gccgtgccct
61  tccccgcgc gctcaccctg ttctcgggat gggattgtag cggcgccgcg gactcggcgg
121 ggatcgcgcg ggaggcggcg gcgtcggcgg cggcgtcggc ggccgagcgg ggctccatgt
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301 gatttgccct ctacaagcgg cccaaggcaa atggtgtcaa acccagcacc gtccatgtga
361 tatccacgcc ccaggcatcc aaggctatca gctgcaaagg tcaacacagt ataccctaca
421 ctttgtcaag gaatcagact gtggtggtgg agtacacaca tgataaggat acggatatgt
481 ttcagggtggg cagatcaaca gaaagcccta tcgacttcgt tgacacagac acgatttctg
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601 ggatcggtgt cgacaggaat gaaccttaca cagcacggat attcgccgcc ggatttgact
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721 tggatgggct cactactaat ggcgtcctgg tgatgcatcc acgagggggc ttcaccgagg
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961 ttcatactcc aactcagaag cacatagaag cctccggcca ggagattaac gccgcccggc
1021 ctcagtgtcc tgtggggctc aacaccctgg ccttcccag catcaacagg aaagagggtg
1081 tggaggagaa gcagccctgg gcatatctca gttgtggcca cgtgcacggg taccacaact
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1261 caactcatgc tttcaactccc tgtggacacg tgtgctcgga gaagtctgca aaatactggt
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1381 cacagctggt tggggagcaa aactgcatca aattaatttt ccaaggcca attgactgac
1441 gcccttgaca gccatctacg actttattaa caggttactg tgaagatttt gccactaact
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LOXL1 cDNA sequence 2 (SEQ ID NO: 27)

NM_005576 Homo sapiens lysyl oxidase-like 1 (LOXL1), mRNA

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CASPR4 cDNA sequence 1 (SEQ ID NO: 28)

NM_033401 Homo sapiens cell recognition protein CASPR4 (CASPR4), transcript variant 1, mRNA

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CASPR4 cDNA sequence 2 (SEQ ID NO: 29)

NM_138994 Homo sapiens cell recognition protein CASPR4 (CASPR4), transcript variant 2, mRNA

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2041 aataagcaag atggaacccc tctgagttgg tgggtaggaa gaaccaatga aacgcaaacc
2101 tactggggag gttcttcgcc tgatcttcaa aaatgtactt gtggattaga gggaaactgc
2161 attgattctc agtattactg caattgtgat gctgaccgga atgaatgggtg atttccatac
2221 gatttcttta tgcaagaaaa agttcattta aaaaaattaa tcaactcaaag tatgtatagc
2281 tagccagata ctgaacaagt tagtgcaatg aagtaattaa ataaaggttt gttttaatg

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GPR50 cDNA sequence (SEQ ID NO: 30)

NM_004224 Homo sapiens G protein-coupled receptor 50 (GPR50), mRNA

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1 tgtttgctgt ctggacctgg ctgctgatcc tgagcctgct gggagatctt aacgatcccc
61 aggagcaaca tggggcccac cctagcgggt cccacccctc atggctgtat tggctgtaag
121 ctaccccagc cagaataccc accggctcta atcatcttta tgttctgcgc gatggtatc
181 accatcgttg tagacctaat cggcaactcc atgggtcattt tggctgtgac gaagaacaag
241 aagctccgga attctggcaa catcttctgtg gtcagtctct ctgtggcoga tatgctgggtg
301 gccatctacc catacccttt gatgctgcat gccatgtcca ttgggggctg ggcctgagc
361 cagttacagt gccagatggg cgggttcac acagggctga gtgtggctgg ctccatcttc
421 aacatcgtag caatcgctat caaccgttac tgctacatct gccacagcct ccagtacgaa
481 cggatcttca gtgtgcgcaa tacctgcac tacctggta tcacctggat catgaccgtc
541 ctggctgtcc tgcctacat gtacattggc accatcgagt acgatctctg cacctacacc
601 tgcattctca atcatctgaa caaccctgtc ttcactgtta ccatcgctctg catccacttc
661 gtcctccctc tcctcatcgt ggggtttctg tacgtgagga tctggaccaa agtgctggcg
721 gccgtgacc ctgcaggcca gaatcctgac aaccaacttg ctgaggttcg caattttcta
781 accatgtttg tgatcttctt cctcttttga gtgtgctggg gccctatcaa cgtgctcact
841 gtcttggtgg ctgtcagtc gaaggagatg gcaggcaaga tccccactg gctttatctt
901 gcagcctact tcatagccta ctcaacagc tgcctcaacg ctgtgatcta cgggctcctc
961 aatgagaatt tccgaagaga atactggacc atcttccatg ctatgcggca ccctatcata
1021 ttcttccctg gcctcatcag tgatattcgt gagatgcagg agggccgtac cctggcccgc
1081 gccctgcccc atgctcgcga ccaagctcgt gaacaagacc gtgcccattg ctgtcctgct
1141 gtggaggaaa ccccgatgaa tgtccggaat gttccattac ctgggtgatg tgcagctggc
1201 caccocgacc gtgcctctgg ccacccaaag cccatttcca gatcctctc tgcctatcgc
1261 aaatctgcct ctaccacca caagtctgtc tttagccact ccaaggctgc ctctggtcac
1321 ctcaagcctg tctctggcca ctccaagcct gcctctgggt accccaagtc tgccactgtc
1381 taccctaagc ctgcctctgt ccatttcaag ggtgactctg tccatttcaa ggggtgactct
1441 gtccatttca agcctgactc tgttcatttc aagcctgctt ccagcaaccc caagccatc
1501 actggccacc atgtctctgc tggcagccac tccaagtctg ccttcagtgc tgccaccagc
1561 caccctaaac ccataagcc agctaccagc catgctgagc ccaccactgc tgactatccc
1621 aagcctgcca ctaccagcca ccctaagccc gctgctgctg acaacccctga gctctctgcc
1681 tcccattgcc cagagatccc tgccattgcc caccctgtgt ctgacgacag tgacctcctc
1741 gactggcctc ctgactgtgc cgtctggccc accaagcctg ctgccagcca gctggagtct
1801 gacaccatcg ctgaccttcc tgacctact gtagtacta ccagtaccaa tgattaccat
1861 gatgtcgtgg ttgttgatgt tgaagatgat cctgatgaaa tggctgtgtg aaaaatgctc
1921 tcgtaggtgg ccaggcagt

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APOL3 cDNA sequence 1 (SEQ ID NO: 31)

NM_145640 Homo sapiens apolipoprotein L, 3 (APOL3), transcript variant alpha/d, mRNA

```

1  agcaggaggg  tgggaccaag  ggtgctgctg  gaccaaggat  gggactgggc  caaggggtggg
61  gctgggaagc  atcctgtttt  gcatgtttga  tcaggagctg  ctgccaaagt  gtgactttca
121  ctttcccttt  tgggttccag  ggtatatctc  agagcctgga  gaacgtgtct  gggtattatg
181  cagatgcacg  gctggagggt  ggatccacac  agctcagaac  agctggatct  tgctcacact
241  ctttcaagag  aagcttcctt  gaaaagaaac  gctttactga  agaggccacc  aaatacttcc
301  gggagagagt  cagcccagtg  catctgcaaa  tcctgctgac  taacaatgaa  gcctggaaga
361  gattcgtgac  tgcggctgaa  ttgccagggg  atgaggcaga  tgctctctac  gaagctctga
421  agaagcttag  aacatatgca  gctattgagg  acgaatatgt  gcagcagaaa  gatgagcagt
481  ttagggaatg  gtttttgaaa  gagtttcccc  aagtcaagag  gaagatccag  gagtccatag
541  aaaagcttcg  tgcccttgca  aatggtat  tg  aagagggtcca  cagaggctgc  accatctcca
601  cacaaccat  cagctccact  ggcgctgcct  ctggcatcat  gtcccttgct  ggtctgtttt
661  tggcaccatt  tacagcaggg  acgagtctgg  cccttactgc  agctggggta  gggctgggag
721  cagcgtctgc  tgtgactggg  atcaccacca  gcctcgtgga  gcactcatat  acatcatcag
781  cagaagctga  agccagcagg  ctgactgcaa  ccagcattga  ccgattgaag  gtatttaagg
841  aagttatgcg  tgacatcaca  cccaacttca  tttcccttct  taataattat  tacgaagcca
901  cagaacttcc  tgggagtga  atccgtgcca  tcaggcaagc  cagagccagg  gcccgactcc
961  ctgtgaccac  ctggcgaaat  tcagctggaa  gtgggtggta  agcagagaga  acgattgcag
1021  gcaccaccgg  ggcagtgaag  agaggagccc  ggatccctgag  tgcgaccact  tcaggcatct
1081  tccttgcaat  ggatgtgggt  aaccttgtat  acgagtcaaa  gcacttgcat  gagggggcaa
1141  agtctgcatc  tgcctgaggg  ctgaggcggg  aggtcagga  gctggaggag  aatctaattg
1201  agctcactca  gatctatcag  cgtctgaaat  catgccatac  ccactgacct  cagaccagtg
1261  cagccagcag  gggagggtgag  ccatacacag  gccacgacaa  aatgcaggca  ttttattagg
1321  gggataaaga  gggcaaggta  aagtttatgg  agctgagtg  tagtgacttt  ggcatttctg
1381  tagctgagca  cagcagggga  ggggttaa  tg  cagatggcaa  gtgcaccaag  gagaaggcag
1441  gaagtctgga  gccttgaata  agggaggaga  ggggactgga  gagtggtggg  aataggaaga
1501  agaaatttcc  tttagactaa  cgaatatatt  ggggggagga  atagagggga  ggtgtgcagg
1561  aaccagcaat  gagaaggcca  ggaaaagaaa  gagctgaaaa  tgcagaaagc  cgaagagtta
1621  gaacttttgg  atacagcaga  agaaacagcg  gctccactac  cgactgccc  ccggttcgat
1681  gtccttccaa  gaatgaagtc  tttccctggg  gatgggtccc  tgccctgtct  ttccagcatc
1741  cactctgtct  tgtcctctg  gaagtgtatc  tcagtcagcc  agtggcttct  tgatgatggc
1801  ggtggaggtg  gtggttgtag  tgtgatggat  cccctttagg  ttattttagg  gtatatgtcc
1861  cctgcttgaa  ccctgaaggc  caggtaatga  gccatggcca  ttgtccccag  ctgaggacca
1921  ggtgtctcta  aaaacccaaa  catcctggag  agtatgagag  aacctaccaa  gaaaaacagt
1981  ctcatctctc  atatacagca  ggcaaagaga  cagaaaatta  actgaaaagc  agtttagaga
2041  ctgggggagg  ccggtatctc  agagccatcc  tgctgagtg  cctgtgtgta  agtccataa
2101  aactcaccta  ctcaccaa

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APOL3 cDNA sequence 2 (SEQ ID NO: 32)

NM_014349 Homo sapiens apolipoprotein L, 3 (APOL3), transcript variant alpha/a, mRNA

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1  agcaggaggg  tgggaccaag  ggtgctgctg  gaccaaggat  gggactgggc  caaggggtggg
61  gctgggaagc  atcctgtttt  gcatgtttga  tcaggagctg  ctgccaaagt  gtgactttca
121  ctttcccttt  tgggttccag  ggtatatctc  agagcctgga  gaacgtgtct  gggtattatg
181  cagatgcacg  gctggagggt  ggatccacac  agctcagaac  agctggatct  tgctcacact
241  ctttcaagag  aagcttcctt  ggacaaaagg  accctgcctt  ggtgtgagag  tgagggcaga
301  gggagctgga  gcaagtagaa  tttctctaaa  taccagctgg  ctggggccca  ggagattaaa
361  aacacccggg  ctaggttggg  cttggcat  tt  gctgacacgc  aaagggattg  cagagatcca
421  gcccctccaa  cctccctctg  tccacagggt  gctcacatcc  agtcccacaa  tttgctttct
481  cctcctcaag  ggtaagaaa  aaaaacgaac  ccttccagtc  aggtcagtga  ctggagagct
541  ccatggaaag  tctctcagtg  accctggctg  tggcaccatg  gactcagaaa  agaaacgctt
601  tactgaagag  gccaccaa  acttccggga  gagagtcagc  ccagtgcatt  tgcaaatcct
661  gctgactaac  aatgaagcct  ggaagagatt  cgtgactgag  gctgaattgc  ccaggatgga
721  ggcagatgct  ctctacgaag  ctctgaagaa  gcttagaaca  tatgcagcta  ttgaggacga
781  atatgtgcag  cagaaagatg  agcagtttag  ggaatgggtt  ttgaaagagt  tcccccaagt
841  caagaggaag  atccaggagt  ccatagaaaa  gcttcgtgct  cttgcaaatg  gtattgaaga

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901 ggtccacaga ggctgcacca tctccaatgt ggtgtccagc tccactggcg ctgcctctgg
961 catcatgtcc cttgctgggtc ttgttttggc accatttaca gcagggacga gtctggccct
1021 tactgcagct ggggtagggc tgggagcagc gtctgtgtgt actgggatca ccaccagcat
1081 cgtggagcac tcatacacat catcagcaga agctgaagcc agcaggctga ctgcaaccag
1141 cattgaccga ttgaaggtat ttaaggaagt tatgctgac atcacacca acttactttc
1201 ccttcttaat aattattacg aagccacaca aaccattggg agtgaaatcc gtgccatcag
1261 gcaagccaga gccaggggccc gactccctgt gaccacctgg cgaatctcag ctggaagtgg
1321 tggtaacga gagagaacga ttgcaggcac caccggggca gtgagcagag gagcccggt
1381 cctgagtgcg accacttcag gcatcttcct tgactggat gtggtcaacc ttgtatacga
1441 gtcaaagcac ttgcatgagg gggcaaagtc tgcatctgct gaggagctga ggcggcaggc
1501 tcaggagctg gaggagaatc taatggagct cactcagatc tatcagcgtc tgaatccatg
1561 ccatacccac tgacccaga ccagtgcagc cagcagggga ggtgagccat acacaggcca
1621 cgacaaaatg caggcatttt attaggggga taaagagggc aaggtaaagt ttatggagct
1681 gagtgttagt gactttggca tttctgtagc tgagcacagc aggggagggg ttaatgcaga
1741 tggcaagtgc accaaggaga aggcaggaat gctggagcct ggaataaggg aggagagggg
1801 actggagagt gtggggaata ggaagaagaa atttccttta gactaacgaa tatattgggg
1861 ggaggaatat aggggaggtg tgcaggaacc agcaatgaga aggccaggaa aagaaagagc
1921 tgaaaatgca gaaagccgaa gagttagaac ttttgatcac agcagaagaa acagcggtc
1981 cactaccgac ctgccccggg ttctgtatcc ttccaagaat gaagtcttcc cctggtgatg
2041 gtccccctgc ctgtctttcc agcatccact ctgtcttctc ctctggaag tgtatctcag
2101 tcagccagtg gcttcttgat gatggcggtg gagtggtggg ttgtagtgtg atggatcccc
2161 tttaggttat ttagggttat atgtcccctg cttgaaccct gaaggccagg taatgagcca
2221 tggccattgt cccacagtga ggaccaggtg tctctaaaaa cccaaacatc ctggagagta
2281 tgcgagaaac taccagaata aacagtctca ttactcatat acagcaggca aagagacaga
2341 aaattaactg aaaagcagtt tagagactgg gggaggccgg atctctagag ccactctgct
2401 gagtgcctgc tgtgtaagtc ctaataaact cactactca ccaa

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APOL3 cDNA sequence 3 (SEQ ID NO: 33)

NM_030644 Homo sapiens apolipoprotein L, 3 (APOL3), transcript variant alpha/b, mRNA

```

1 agcaggaggg tgggaccaag ggtgctgctg gaccaaggat gggactgggc caagggtggg
61 gctgggaagc atcctgtttt gcatgtttga tcaggagctg ctgccaaagt gtgactttca
121 ctttcccttt tgggttccag ggtatatctc agagcctgga gaacgtgtct gggtattatg
181 cagatgcacg gctggaggtg ggatccacac agctcagaac agctggatct tgctcacact
241 ctttcaagag aagcttccct ggacaaaagg accctgcctt ggtgtgagag tgagggcaga
301 gggagctgga gcaagttaga tttctctaaa taccagctgg ctggggccca ggagattaaa
361 aaacacccgg ctagggttaa gaaaaaaaac gaaccttcc agtcagggtc gtgactggag
421 agtcccatgg aaagtctctc agtgacctgg ctgctggcac catggactca gaaaagaaac
481 gctttactga agaggccacc aaatacttcc gggagagagt cagcccagtg catctgcaaa
541 tcctgctgac taacaatgaa gcctggaaga gattcgtgac tgcggtgaa ttgccaggg
601 atgaggcaga tgctctctac gaagctctga agaagcttag aacatatgca gctattgagg
661 acgaatatgt gcagcagaaa gatgagcagt ttagggaatg gtttttgaaa gattttcccc
721 aagtcaagag gaagatccag gagtccatag aaaagcttcc tgcccttgca aatggtattg
781 aagagggtcca cagaggctgc accatctcca atgtggtgtc cagctccact ggcgctgcct
841 ctggcatcat gtcccctgct ggtcttgttt tggcaccatt tacagcaggg acgagctctg
901 ccttactgac agctggggtg gggctgggag cagcgtctgc tgtgactggg atcaccacca
961 gcatcgtgga gcactcatac acatcatcag cagaagctga agccagcagg ctgactgcaa
1021 ccagcattga ccgattgaag gtatttaagg aagttatgct tgacatcaca cccaacttac
1081 tttcccttct taataattat tacgaagcca cacaaccatc tgggagtgaa atccgtgcca
1141 tcaggcaagc cagagccagg gcccgactcc ctgtgaccac ctggcgaaac tcagctggaa
1201 gtggtggtca acgagagaga acgattgcag gcaccaccog ggcagtgagc agaggagccc
1261 ggatcctgag tgcgaccact tcaggcatct tccttgcact ggatgtgggtc aaccttgat
1321 acgagtcaaa gcacttgcat gagggggcaa agtctgcact tgctgaggag ctgaggcggc
1381 aggtcagga gctggaggag aatctaattg agctcactca gatctatcag cgtctgaatc
1441 catgccatac ccactgacct cagaccagtg cagccagcag gggaggtgag ccatacacag
1501 gccacgacaa aatgcaggca ttttattagg gggataaaga gggcaaggta aagtttatgg
1561 agctgagtgt tagtgacttt ggcatttctg tagctgagca cagcagggga ggggttaatg
1621 cagatggcaa gtgcaccaag gagaaggcag gaatgctgga gcctggaata agggaggaga
1681 ggggactgga gagtgtgggg aataggaaga agaaatttcc tttagactaa cgaatatatt
1741 ggggggagga atagagggga ggtgtgcagg aaccagcaat gagaaggcca ggaaaagaaa
1801 gagtgaataa tcagaaaagc cgaagagttg gaacttttgg atacagcaga agaaacagcg
1861 gctccactac cgacctgccc ccggttcgat gtccctccaa gaatgaagtc tttccctggg

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1 921 gatgggtcccc tgccctgtct ttccagcatc cactctgtct tgtcctcctg gaagtgtatc
1 981 tcagtcagcc agtggcttct tgatgatggc ggtggagggtg gtgggtgtag tgtgatggat
2 041 ccccttttagg ttatttaggg gtatatgtcc cctgcttgaa Ccctgaaggc caggtaatga
2 101 gccatggcca ttgtcccgag ctgaggacca ggtgtctcta aaaacccaaa catcctggag
2 161 agtatgcgag aacctaccaa gaaaaacagt ctcttactc atatacagca ggcaaagaga
2 221 cagaaaatta actgaaaagc agtttagaga ctgggggagg Ccggatctct agagccatcc
2 281 tgctgagtgc cctgtgtgta agtcctaata aactcaccta ctcaccaa

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APOL3 cDNA sequence 4 (SEQ ID NO: 34)

NM_030644 Homo sapiens apolipoprotein L, 3 (APOL3), transcript variant alpha/c, mRNA

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1 agcaggaggg tgggaccaag ggtgctgctg gaccaaggat gggactgggc caaggggtggg
61 gctgggaagc atcctgtttt gcatgtttga tcaggagctg ctgccaagtt gtgactttca
121 ctttcccttt tgggttccag ggtatatctc agagcctgga gaacgtgtct ggttattatg
181 cagatgcacg gctggagggtg ggatccacac agctcagaac agctggatct tgctcacact
241 ctttcaagag aagcttccct gggttaagaa aaaaaacgaa Cccttccagt caggtcagtg
301 actggagagc tccatggaaa gtctctcagt gacctggctg ctggcaccat ggactcagaa
361 aagaaacgct ttactgaaga ggccaccaa tacttccggg agagagtcag cccagtgcac
421 ctgcaaatac tgctgactaa caatgaagcc tggagagat tctgtactgc ggctgaattg
481 cccagggatg aggcagatgc totctacgaa gctctgaaga agcttagaac atatgcagct
541 attgaggacg aatatgtgca gcagaaagat gacagttta gggaaatggt tttgaaagag
601 tttccccaag tcaagaggaa gatccaggag tccatagaaa agcttcgtgc ccttgcaaat
661 ggtattgaag aggtccacag aggtctgcac atctccaatg tgggtgtccag ctccactggc
721 gctgcctctg gcatcatgtc ccttgctggt cttgttttgg Caccatttac agcaggggacg
781 agtctggccc ttactgcagc tggggtaggg ctgggagcag Cgtctgctgt gactgggatc
841 accaccagca tctgtgagca ctcatacaca tcacagcag aagctgaagc cagcaggctg
901 actgcaacca gcattgaccg attgaaggta ttaaggaag ttatgcgtga catcacacc
961 aacttacttt cccttcttaa taattattac gaagccacac aaaccatttg gagtgaatc
1 021 cgtgccatca ggcaagccag agccaggggc cgactocctg tgaccacctg gcgaatctca
1 081 gctggaagtg gtggtcaagc agagagaacg attgcaggca Ccaccggggc agtgagcaga
1 141 ggagcccga tccctgagtc gaccattca ggcattctcc ttgcaactga tgggtcaac
1 201 cttgtatacg agtcaaagc cttgcattag ggggcaaagt ctgcatctgc tgaggagctg
1 261 aggcggcagg ctgaggagct ggaggagaat ctaatggagc tcaactcagat ctatcagcgt
1 321 ctgaatccat gccataccca ctgacccag accagtgcag Ccagcagggg aggtgagcca
1 381 tacacaggcc acgacaaaat gcaggcattt tattaggggg ataaagaggg caaggtaaag
1 441 tttatggagc tgagtgttag tgactttggc atttctgtag ctgagcacag caggggaggg
1 501 gttatggcag atggcaagt gaccaaggag aaggcaggaa tgctggagcc tggaaataag
1 561 gaggagaggg gactggagag tgtggggaat aggaagaaga aatttccttt agactaacga
1 621 atatatggg gggaggaata gaggggaggt gtgcaggaa cagcaatgag aaggccagga
1 681 aaagaaagag ctgaaaatgc agaaagccga agagttagaa Cttttggata cagcagaaga
1 741 aacagcggct ccactaccga cctgccccgc gttcgatgtc cttccaagaa tgaagtcttt
1 801 ccctgggtgag ggtccctgc cctgtctttc cagcatccac tctgtcttgt cctcctggaa
1 861 gtgtatctca gtcagccagt ggcttcttga tgatggcggt ggaggtggtg gttgtagtgt
1 921 gatggatccc ctttaggtta tttaggggta tatgtcccct gcttgaaccc tgaaggccag
1 981 gtaatgagcc atggccattg tccccagctg aggaccaggt gtctctaaaa acccaaacat
2 041 cctggagagt atgcgagaac ctaccaagaa aaacagtctc attactcata tacagcaggc
2 101 aaagagacag aaaattaact gaaaagcagt ttagagactg ggggaggccg gatctctaga
2 161 gccatcctgc tgagtgcctt gtgtgtaagt cctaataaac tcacctactc accaa

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APOL3 cDNA sequence 5 (SEQ ID NO: 35)

NM_145641 Homo sapiens apolipoprotein L, 3 (APOL3), transcript variant beta/a, mRNA

```

1 actctgggga aaggagggtg caaccacatg taaattttat tataatgatg gtataatgaa
61 cttgggggtg octgagggca tgtttttgtg ttactgggca tgtgcccctt taggagactt
121 ccacctgtgc cttactttct ctttcttttg gatgtgctgg ccacagactt taccaaaaac
181 tccatccatt aggatggcat taggacgggt ctggggctaa acttaggttg gccaggggct
241 gtttactgt cagcctttct actctctttt cttaccact cctagctgct aatgtctatt
301 taactaccta atatttcccc ctttagagaa aaaaagccaa atttttgggt agatcgggtg

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361 caat taatct ggctacttcc tgctgacaag aggcagtggt aataattggg ttctcttttt
421 tgct ctcttg tagctggtag gttgggcaga gaaaagtggt ggccatccaa gggggccacg
481 taga tatcag acatgggtga gacctcgcg taacctgtg tagaatcatt tggagtttta
541 tga ttctag gtgggaagaa acaaaacaac cttgtaaatc aaatgagcat cgtttgaaag
601 ctat aagttg tataaagctg ttttaggacc aagaaagggg gctaaccagg aaaaccagga
661 ccag ttgtta aatttccacc agtcaaagcc tcctgaaact ctgttttcca ttaacttggt
721 ggcc ctgtct gtaatttttt taagttgggt tgcaactttac ctgattgggt gatgaaaaca
781 gcaa tgttta tcaagtgttg cacaagctcc cccttgattg gctgtgagca aattaaaagc
841 tcat caattt cataagacta tgcttgctaa tgaagcaatt tgttctgaaa gggatttgac
901 ctgg ttagtt agattaataa tttgttgagt aatttttaag aagagtctct gggcagtaaa
961 aatggagttta aggaggtcct ccagttcccg tgccaatacc agccagaacg ccaattatag
1021 tcag tgctgt taaaactcct ctttcagttt taccagattg agcgtgtata gggaggggaa
1081 tgct atcgat aagagttagt ttggggatga tgtaaaactag ggccaaatcc ccgtttaatt
1141 agca gacaag cagagatatg ccttgtttct atacaaaaat gtgatttgct atgttaagac
1201 aaat atcaac agtgatacta aagtaggggt tttccatgct gtgtaagtct gctttaatac
1261 cctc agaagt ggaagtcaag gctagttcat gtaatggggg aacacaggca gtacttgaca
1321 gaat gaaaga ggaatcaaaa gcccaattag aggaaggagt gatgggatcc caaccaatat
1381 tgtg aaatta tggggagctg cagttttttg caatgatttt gccgaagtt gtgagactga
1441 aacc agaagt tgttatgttt aaaatgatat tctggtgtgg gtctgggtaa aagggtagat
1501 ccag aatagc tggcttcttt ccacatagtg gttctgttgg ggggcttggg aaatgaataa
1561 aaca caaaga agaattagaa tatcaggtga aggtagcagg tgctcctggc agaagaacct
1621 acat aaggaa gtgtccagaa gccacacagg gtatatctca gacctggag aacgtgtctg
1681 gtta ttatgc agatgcacgg ctggaggttg gatccacaca gctcagaaca gctggatcct
1741 gctc acactc tttcaagaga agcttccttg aaaagaaacg cttactgaa gaggccacca
1801 aata cttccg ggagagagtc agcccagtc atctgcaaat cctgctgact aacaatgaag
1861 cctg gaagag attcgtgact gcggctgaat tgcccaggga tgaggcagat gctctctacg
1921 aagc tctgaa gaagcttaga acatatgcag ctattgagga cgaatatgtg cagcagaaag
1981 atga gcagtt tagggaatgg tttttgaaag agtttcccca agtcaagagg aagatccagg
2041 agtc cataga aaagctctgt gcccttgcaa atggtattga agaggtccac agaggctgca
2101 ccat ctccaa tgtggtgtcc agctccactg gcgctgcctc tggcatcatg tcccttgctg
2161 gtct tgtttt ggcaccattt acagcaggga cgagtctggc ccttactgca gctggggtag
2221 ggct gggagc agcgtctgct gtgactggga tcaccaccag catcgtggag cactcataca
2281 catc atcagc agaagctgaa gccagcaggc tgactgcaac cagcattgac cgattgaag
2341 tatt taagga agttatgctg gacatcacac ccaacttact ttcccttctt aataattatt
2401 acga agccac acaaaccatt gggagtgaat tccgtgccat caggcaagcc agagccaggg
2461 cccg actccc tgtgaccacc tggcgaatct cagctggaag tggtggtcaa gcagagagaa
2521 cgat tgcagg caccacccgg gcagttagca gaggagcccg gatcctgagt gcgaccactt
2581 cagg catctt ccttgcactg gatgtggtca accttgtata cgagtcaaag cacttgcatt
2641 aggg ggcaaa gcttgcactc gctgaggagc tgaggcggca ggctcaggag ctggaggaga
2701 atct aatgga gctcactcag atctatcagc gtctgaatcc atgccatacc cactgacccc
2761 agac cagtgc agccagcagg ggaggtgagc catacacagg ccacgacaaa atgcaggcat
2821 tttt ttaggg ggataaagag ggcaaggtaa agtttatgga gctgagtgtt agtgactttg
2881 gcat tctctg agctgagcac agcaggggag gggttaatgc agatggcaag tgcaccaagg
2941 agaa ggcagg aatgctggag cctggaaataa gggaggagag gggactggag agtggtggga
3001 atag gaagaa gaaatttctt ttagactaac gaatatattg gggggaggaa tagaggggag
3061 gtgt gcagga accagcaatg agaaggccag gaaaagaaa agctgaaaat gcagaaagcc
3121 gaag agttag aacttttgga tacagcagaa gaaacagcgg ctccactacc gacctgcccc
3181 cgtt tcatag tccctccaag aatgaagtct ttccctgggt atgggtccct gccctgtctt
3241 tcca gcatcc actctgtctt gtccctcctg aagtgtatct cagtcaagcca gtggcttctt
3301 gatg atggcg gtggaggtgg tggttgtagt gtgatggatc ccttttaggt tatttagggg
3361 tata tgtccc ctgcttgaa cctgaaggcc aggtaatgag ccatggccat tgtccccagc
3421 tgag gaccag gtgtctctaa aaacccaaag atcctggaga gtatgcgaga acctaccaag
3481 aaaa acagtc ctactactca tatacagag gcaaagagac agaaaaataa ctgaaaagca
3541 gttt agagac tgggggaggg cggatctcta gagccatcct gctgagtgcc ctgtgtgtaa
3601 gtcc taataa actcacctac tcaccaa

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APOL3 cDNA sequence 6 (SEQ ID NO: 36)

NM_145642 Homo sapiens apolipoprotein L, 3 (APOL3), transcript variant beta/a, mRNA

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1 actc tgggga aaggagggta caaccacatg taaattttat tataatgatg gtataatgaa
61 ctgtgggtga cctgagggca tgtttttgtg ttactgggca tgtgccctt taggagactt
121 ccac ctgtgc cttactttct ctttcttttg gatgtgctgg ccacagactt taccaaaaaa

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181 tccatccatt aggatggcat taggacgggt ctggggcetaa acttaggtgg gc cagggggt
241 gtttctactgt cagcctttct actctctttt cttaccact cctagctgt aa tgtctatt
301 taactacctt atatttcccc ctttagagaa aaaaagccaa atttttgggt agatcggtga
361 caattaatct ggctacttcc tgctgacaag aggcagtggg aataattggg tt ctcttttt
421 tgctctcttg tagctggtag gttgggcaga gaaaagtggg ggccatccaa ggggcccacg
481 tagatatcag acatgggtga gacctcgcg taaccttgtg tagaatcatt tggagtttta
541 tggattctag gtgggaagaa acaaaacaac cttgtaaatac aaatgagcat cgtttgaaag
601 ctataagttg tataaagctg ttttaggacc aagaaagggg gctaaccagg aa aaccagga
661 ccagttgtta aatttccacc agtcaaagcc tcctgaaact ctgttttcca tt aacttgtt
721 ggccctgtct gtaatttttt taagttgggt tgcactttac ctgattgggt ga tgaaaaca
781 gcaatgttta tcaagtgttg cacaagctcc cccttgattg gctgtgagca aa ttaaaagc
841 tcatcaattt cataagacta tgcttgctaa tgaagcaatt tgttctgaaa ggggtattgac
901 ctggttagtt agattaataa tttgttgagt aatttttaag aagagtttct gggcagtaaa
961 aatggagtta aggaggtcct ccagttcccg tgccaatacc agccagaacg cc aattatag
1021 tcagtgtctg taaaactcct ctttcagttt taccagattg agcgtgtata gggaggggaa
1081 tgctatcgat aagagttagt ttggggatga tgtaaactag ggccaaatcc ccgtttaatt
1141 agcagacaag cagagatatg ccttgtttct atacaaaaat gtgatttgtc atgttaagac
1201 aaatatcaac agtgatacta aagtaggggt tttccatgct gtgtaagtct gctttaatac
1261 cctcagaagt ggaagtcaag gctagttcat gtaatggggg aacacaggca gt acttgaca
1321 gaatgaaaga ggaatcaaaa gcccaattag aggaaggagt gatgggatcc caaccaatat
1381 tgtgaaatta tggggagctg cagttttttt caatgatatt gcccgaggt gtgagactga
1441 aaccagaagt tgttatgttt aaaatgatat tctggtgtgg gtctggggaa aagggtagat
1501 ccagaatagc tggcttcttt ccacatagtg gttctgttgg ggggcttggg aaatgaataa
1561 aacacaaga agaattagaa tatcagggtat tatctcagag cctggagaac gtgtctggtt
1621 attatgcaga tgcacggctg gaggtgggat ccacacagct cagaacagct ggatcttgc
1681 cacactcttt caagagaagc ttccttgaaa agaaacgctt tactgaagag gc caccaaat
1741 acttccggga gagagtcaag ccagtgcac tgcaaatcct gctgactaac aa tgaagcct
1801 ggaagagatt cgtgactgag gctgaattgc ccagggatga ggcagatgct ct ctacgaag
1861 ctctgaagaa gcttagaaca tatgcagcta ttgaggacga atatgtgcag cagaaagatg
1921 agcagtttag ggaatgggtt ttgaaagagt tcccccaagt caagaggaag at ccaggagt
1981 ccatagaaaa gcttcgtgcc cttgcaaatg gtattgaaga ggtccacaga gg ctgcacca
2041 tctccaatgt ggtgtccagc tccactggcg ctgcctctgg catcatgtcc ct tgcctggtc
2101 ttgttttggc accatttaca gcaggagcga gtctggccct tactgcagct ggggtagggc
2161 tgggagcagc actggtgtg actgggatca ccaccagcat cgtggagcac tcatacacat
2221 catcagcaga agctgaagcc agcaggctga ctgcaaccag cattgaccga tt gaaggtat
2281 ttaaggaagt tatgcgtgac atcacacca acttaacttt ccttcttaat aa ttattacg
2341 aagccacaca aaccattggg agtgaaatcc gtgccatcag gcaagccaga gc cagggccc
2401 gactccctgt gaccacctgg cgaatctcag ctggaagtgg tggccaagca ga gagaacga
2461 ttgcaggcac caccgggca gtgagcagag gagcccgat cctgagtgcg ac cacttcag
2521 gcatcttctc tgcactggat gtggtcaacc ttgtatacga gtcaaagcac tt gcatgagg
2581 gggcaaagtc tgcactgtct gaggagctga ggcggcaggc tcaggagctg ga ggagaatc
2641 taatggagct cactcagatc tatcagcgtc tgaatccatg ccatacccac tg accccaga
2701 ccagtgcagc cagcagggga ggtgagccat acacaggcca cgacaaaatg caggcathtt
2761 attaggggga taaagagggc aaggtaaagt ttatggagct gagtgttagt ga ctttggca
2821 tttctgtagc tgagcacagc aggggagggg ttaatgcaga tggcaagtgc ac caaggaga
2881 aggcaggaat gctggagcct ggaataaggg aggagagggg actggagagt gt ggggaata
2941 ggaagaagaa atttcttta gactaacgaa tatattgggg ggaggaaatag aggggaggtg
3001 tgcaggaacc agcaatgaga aggccaggaa aagaaagagc tgaaaatgca ga aagccgaa
3061 gagttagaac ttttgatac agcagaagaa acagcggctc cactaccgac ct gcccocgg
3121 ttcgatgtcc ttccaagaat gaagtctttc cctggtgatg gtccctgcc ctgtctttcc
3181 agcatccact ctgtcttgtc ctcttggaag tgtatctcag tcagccagtg gc ttcttgat
3241 gatggcggtg gaggtgggtg ttgtagtgtg atggatcccc tttaggttat tt aggggtat
3301 atgtcccctg cttgaaccct gaaggccagg taatgagcca tggccattgt cc ccagctga
3361 ggaccagggtg tcttaaaaaa cccaaacatc ctggagagta tgcgagaacc ta ccaagaaa
3421 aacagtctca ttactcatat acagcaggca aagagacaga aaattaactg aa aagcagtt
3481 tagagactgg gggaggccgg atctctagag ccatacctgt gagtgcctg tg tgtaagtc
3541 ctaataaact cacctactca ccaa

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[0347] Following are amino acid sequences *PADI2* (SEQ ID NO: 37), *APOB* (SEQ ID NO: 38), *IL1RL2* (SEQ ID NO: 39), *IL1RL1* (SEQ ID NO: 40-42), *WASPI* (SEQ ID NO: 20), *ADAMTS2* (SEQ ID NO: 43-44), *BVES* (SEQ ID NO: 23-24), *TM7SF3* (SEQ ID NO: 25), *PELI2* (SEQ ID NO: 26),

LOXL1 (SEQ ID NO: 27), *CASPR4* (aka *CNTNAP4*) (SEQ ID NO: 28-29), *GPR50* (SEQ ID NO: 30), and *APOL3* (SEQ ID NO: 31-36)..

PADI2 amino acid sequence (SEQ ID NO: 37)

NP_031391 peptidyl arginine deiminase, type II; protein arginine deiminase [Homo sapiens]

MLRERTVRLQYGSRVEAVYVLGTYLWTDVYSAAPAGAQTFSCLKHSEHVWVEVVRDGEAE EVA
TNGKQRWLLSPS TTLRV TMSQASTEASSDKVTNYYDEEGSIPIDQAGLFLTAIEISLDVDADRD
GVVEKNNPKKASWTWGPEGQGAILLVNCDRETPWLPKEDCRDEKVYSKEDLKDMSQMILRTK
GPDRLPAGYEIVLYISMSDSKVGVFYVENPFFGQRYIHILGRRKLYHVVKYTGGS AELLFFVEG
LCFPDEGFSGLVSIHVSLL EYMAQDIPLTPIFTDTVIFRIAPWIMTPNILPPVSVFVCCMKDNYLFL
KEVKNLVEKTNCELKVCFQYLNRGDRWIQDEIEFGYIEAPHKGFPVVLDSPRDGNLKD FPKEL
LGPDFGYVTREPLFESVTS LDSFGNLEVSPPVTVNGKTYPLGRILIGSSFPLSGGRRMTKVVRDFL
KAQQVQAPVELYSDWLT VGHVDEFMSFVPIPGTKKFLLLMASTSACYKLFREKQKDGHGGEAIM
FKGLGGMSSKRITINKILSNESLVQENLYFQRCLDWNRDILKKELGLTEQDIIDLPA LFKMDEDH
RARAFFPNMVMNMIVLDKDLGIPKFPGPQVEECCLEMHV RGLLEPLGLECTFIDDISAYHKFLGE
VHCGTNVRRKPF TFKWLHMVP

APOB amino acid sequence (SEQ ID NO: 38)

NP_000375 apolipoprotein B precursor; apoB-100; apoB-48 [Homo sapiens]

MDPPRPALLALLALPALLLLLLAGARAE EEMLENVSLVCPKDATR FKHRLK YTYNYEAE SSSGV
PGTADSR SATRNCKVELEV PQLCSFILKTSQCTLKEVYGFNPEGKALLKKTKNSEEF AAAMSR Y
ELKLA IPEGKQVFLYPEKDEPTYILNIKRGII SALLVPPETEEAKQVLF LDTVY GNCSTHFTVKTRK
GNVATEISTERDLGQCDR FKPIRTGISPLALIKGMTRPLSTLISSSQSCQYTLD AKRKHVAE AICKE
QHLFLPFSYNNK YGMVAQVTQTLKLEDTPKINSRFFGEGTKKMGLAFESTK STSPPKQAEAVLK
TLQELKKLTISEQNIQRANLFNKL VTEL RGLSDEAVTSLLPQLIEVSSPITLQALVQCGQPQCSTHI
LQWLKR VHANPLLIDVV TYLVALIPEPSAQLREIFNMARDQRSRATLYALSHAVNNYHKTNPT
GTQELLDIANYLMEQIQDDCTGDEDYTYLILRVIGNMGQTMEQLTPELKSSILKCVQSTKPSLMI
QKAAIQA LRKMEPKDKDQEVLLQTF LDDASPGDKRLAAYLMLMRSPSQADINKIVQILPWEQN
EQVKNFVASHIANILNSEELDIQDLKKLVKEALKESQLPTVMDFRKF SRNYQLYKSVSLPSLDPA
SAKIEGNLIFDPNNYLPKESMLKTTLTA FGFA SADLIEIGLEGKGFEPTLEALFGKQGFFPDSVNK
ALYVWNGQVPDGVSKVLVDHFGYTKDDKHEQDMVNGIMLSVEKLIKDLK SKEVPEARAYLRI
LGEELGFASLHDLQLLGKLLLMGARTLQGIPQMIGE VIRKGSKNDFFLHYIFMENAFELPTGAGL
QLQISSSGVIAPGAKAGVKLEV ANMQAELVAKPSVSVEFVTNMGIIPDFARSGVQMNTNFFHES
GLEAHVALKAGK LKFIIPSPKRPVKLLSGGNTLHLVSTTKTEVIPPLIENRQS WSVCKQVFPGLNY
CTSGAYSNASSTDSASYYP LTGDRLELELRPTGEIEQYSVSATYELQREDRALVDTLKFVTQAE
GAKQTEATMTFK YNRQSM TLSSEVQIPDFDVLGTLRVNDESTE GKTSYRLTLDIQNK KITEVA
LMGHLSCDTKEERKIKGVISIPRLQAEARSEILAHWSPAKLLLQMDSSATAY GSTVSKRVAWHY
DEEKIEFEWNTGTNVDTKKMTSNFPVDLS DYPKSLHMYANRLDHRVPETDMTFRHVGSKLIV
AMSSWLQKASGSLPYTQTLQDHLNSLKEFN LQNMGLPDFHIPENLFLKSDGRVKYTLNKNLSKI
EIPLPFGGKSSRD LKMLETVRTPALHFKSVGFHLPSREFQVPTFTIPKLYQLQVPLLGVLDLSTNV
YSNLYNWSASYS GGNTSTDHFS LRARYHMKADSVVDLLSYNVQSGGETTYD HKNTFTLSCDGS
LRHKFLDSNIKFSHVEKLGNNPVSKGLLIFDASSWGPQMSASVHLD SKKKQHLFVKEVKIDGQ
FRVSSFYAKGTYGLSCQRDPNTGRLNGESNLRFNSSYLQGTNQTGRYEDGTLSTSTSDLQSGII
KNTASLKYENYELTLKSDTNGKYKNFATSNKMDMTFSKQNALLRSEYQADYESLRFFSLLSGSL
NSHGLELNADILGTDKINS GAHKATLRIGQDGISTSATTNLKCSLLVLENELNAELGLSGASMKL
TTNGRFREHNAK FSLDGKAALTELSLGSAYQAMILGVDSKNIFNFKVSQEG LKLSNDMMGSYA
EMKFDHTNSLNLAGLSLDFSSKLDNIYSSDKFYKQTVNLQLQPYSLVTTLNSDLKYNALDLTN

GKLRLEPLKLHVAGNLKGAYQNNEIKHIYAISAAALSASYKADTVAKVQGVESHRLNTDIAGL
 ASAIMSTNYSNDSLHFSNVFRSVMAPFTMTIDAHTNGNGKLALWGEHTGQLYSKFLKAEPL
 AFTFSHDYKGSTSHHLVSRKSISA_ALEHKVSALLTPAEQTGTWKLKTQFNNNEYSQDLDAYNTK
 DKIGVELTGRTLADLTLLDSPKVP_LLLSEPINIIDALEMRAVEKPEFTIVAFVKYDKNQDVHSI
 NLPFFETLQEYFERNRQTIIVVVENVQRNLKHINIDQFVRKYRAALGKLPQQANDYLSNFNWER
 QVSHAKEKLTALTKKYRITENDIQIALDDAKINFNEKLSQLQTYMIQFDQYIKDSYDLHDLKIAIA
 NIIDEIIEKLKSLDEHYHIRVNLVK TIHDLHLFIENIDFNKSGSSTASWIQNVDTKYQIRIQIQEKLQ
 QLKRIHQNIDIQHLAAGLKKQHIEA IDVRVLLDQLGTTISFERINDVLEHVKHVFVNLIGDFEVAEKI
 NAFRAKVHELIEREYVDQQIQVLMMDKLVELTHQYKLKETIQKLSNVLQQVKIKDYFEKLVGFID
 DAVKKLNELSFKTFIEDVNKFLDMLIKKLKSFQYHQFVDETNDKIREVTQRLNGEIQ_ALELPQKA
 EALKLFLEETKATVAVYLESQDTKITLINWLQEALSSASLAHMKAKFRETLEDTRDRMYQMD
 IQQELQRYLSLVGGVYSTLVYISDWWTAAKNLTDFAEQYSIQDWAKRMKALVEQGFTVPEI
 KTILGTMPAFEVSLQALQKATFQT_PDFIVPLTDLRIPSVQINFKDLKNIKIPSRFSTPEFTILNTFHIP
 SFTIDFVEMKVKIIRTIDQMENSELQWPVPDIYLRDLKVEDIPLARITLPDFRLPEIAIPEFIPTLNL
 NDFQVPDLHIPEFQLPHISHTIEVP_TFGKLYSILKIQSPLFTLDANADIGNGTTSANEAGIAASITAK
 GESKLEVLNFDQANAQLSNPKINPLALKESVKFSSKYLRTEHGSEMLFFGNAIEGKSNTVASLH
 TEKNTLELSNGVIVKINNQLTLDSTNTKYFHKLNIPKLDFFSSQADLRNEIKTLLKAGHLAWTSSGK
 GSWKWACPRFSDEGTHESQISFTIEGPLTSFGLSNKINSKHLRVNQNLVYESGSLNFSKLEIQSQV
 DSQHVGHSVLTAKGMALFGEKG_AEFTGRHDAHLNGKVIGTLKNSLFFSAQPFEITASTNNEGNL
 KVRFPRLRTGKIDFLNNYALFLSP_SAAQASWQVSARFNQYKYNQNFSAAGNNENIME_AHVGINGE
 ANLDFLNIPLTIPEMRLPYTIITTP_LKDFSLWEKTGLKEFLKTTKQSFDSLVAQYKK_NKHRHSIT
 NPLAVLCEFISQSIKSFDRHFEKNR_NNALDFVTKSYNETKIKFDKYKAEKSHDELPRTFQIPGYTV
 PVVNVEVSPFTIEMSAFGYVFPKA_VSMPSFSILGSDVRVPSYTLILPSLELPVLHVPRNLKLSLPHF
 KELCTISHIFIPAMGNITYDFSFKSSVITLNTNAELFNQSDIVAHLLSSSSSVIDALQYKLEGTTRLT
 RKRGLKLATALSLSNKFVEGSHNSTVSLTTKNMEVSVAKTTKAEIPILRMNFKQELNGNTKSKP
 TVSSSMEFKYDFNSSMLYSTAKG_AVDHKL_SLESLSYFSIESSTKGDVKGSVLSREYSGTIASEAN
 TYLNSKSTRSSVKLQGTSKIDDIWNLEVKENFAGEATLQRIYSLWEHSTKNHLQLEG_LFFTNGEH
 TSKATLELSPWQMSALVQVHASQPSSFHDFPDLGQEVALNANTKNQKIRWKNEVRTHSGSFQSQ
 VELSNQDEKAHLDIAGSLEGHLRFLKNILPVYDKSLWDFLKLDVTTSIGRRQHRLRVSTAFVYTK
 NPNGYSFIPVKVLADKFITPGLKL_NDLNSVLVMPFTHVPFTDLQVPSCKLDLFREIQIYKKLRTSS
 FALNLPTLPEVKFPFVDVLT_KYSQPEDSLIPFFEITVPESQLTVSQFTLPKSVSDGIAALDLNAVAN
 KIADFELPTIIVPEQTIEIPSIKFSVP_AGIVIPSFQALTARFEVDSPVYNATWSASLKNKA_DYVETVL
 DSTCSSTVQFLEYELNVLGTHKIEDGT_LASKTKGT_LAHRDFS_AEYEEDGKFEG_LQEWEGKAHLN
 IKSPAFTDLHLRYQKDKKGISTSA_ASPA_VGTVGMMDDEDDDFSKWNFYYSPOSSPD_KKLTIFFT
 ELRVRESDEETQIKVNWEEEAASGLTSLKDNVPKATGVLYDYVNKYHWEHTGLTLREVSSKL
 RRNLQNNAEWVYQGAIRQIDDID_VRFQKAASGTTGT_YQEWKDKAQNL_YQELLTQEGQASFGQ
 LKDNVFDGLVRVTQKFHMKVKHLIDSLIDFLNFRFQFPKPGIYTREELCTMFIREVGTVLSQV
 YSKVHNGSEILFSYFQDLVITLPFELRKHKLIDVISMYRELLKDL_SKEAQEVFKAIQSLKTTEVLR
 NLQDLLQFIFQLIEDNIKQLKEMKFTYLINYIQDEINTIFNDYIPYVFKLLKENLCLNLHKFNEFIQ
 NELQEASQELQQIHQYIMALREEY_FDPSIVGWTVKY_YELEEKIVSLIKNLLVALKDFHISEYTVSAS
 NFTSQLSSQVEQFLHRNIQEYLSIL_TDPDGKGKEKIAELSAQAQEIISQAIA_TKKIISD_YHQQFRY
 KLQDFSDQLSDYYEKFIAESKRLIDLSIQNYHTFLIYITELLKKLQSTTVMNPPYMKLA_PGELTIIL

IL1RL2 amino acid sequence (SEQ ID NO: 39)

NP_003845 interleukin 1 receptor-like 2 precursor; interleukin-1 receptor-related protein 2 [Homo sapiens]

MWSLLLCGLSIALPLSVTADGCKDIFMKNEILSASQPFAFNCTFPPTSSEVSVTWYKNSSKIPVS
 KIIQSRIHQDETWILFLPMEWGDSGVYQCVIKGRDSCHRIHVNLTVFEKHWCDTSIGGLPNLSDE
 YKQILHLGKDDSLTCHLHFPKSCVLGPIKWYKDCNEIKGERFTVLETRLLVSNVSAEDRGNYAC
 QAILTHSGKQYEVLNGITVSITERAGYGGSVPKIIPKNHSIEVQLGTTLIVDCNVTDTKDNTNLR

CWRVNNTLVDDYYDESKRIREGVETHVSFREHNLYTVNITFLEVKMEDYGLPFMCHAGVSTAY
 IILQLPAPDFRAYLIGGLIALVAVAVSVVYIYNIFKIDIVLWYRSAFHSTETIVDGKLYDAYVLYPK
 PHKESQRHAVDALVLNILEVLERQCGYKLFIFGRDEFPGQAVANVIDENVKLCRRLIVIVVPESL
 GFGLLKNLSEEQIAVYSALIQDGMKVILIELEKIEDYTMPESIQYIKQKHGAIRWHGDFTEQSQC
 MKTKFWKTVRYHMPPRRCRPFPPVQLLQHTPCYRTAGPELGSRKKCTLTTG

IL1RL1 amino acid sequence 1 (SEQ ID NO: 40)

NP_057316 interleukin 1 receptor-like 1 isoform 1 precursor; interleukin 1 receptor-related protein; homolog of mouse growth stimulation-expressed gene ; ST2 protein [Homo sapiens]

MGFWILAILTILMYSTAAKFSKQSWGLENEALIVRCPRQGKPSYTVDWYYSQTNKSIPTQERNR
 VFASGQLLKFLPAAVADSGIYTCIVRSPTFNRTGYANVTIYKKQSDCNVPDYLMYSTVSGSEKNS
 KIYCPTIDLYNWTAPLEWFKNCQALQGSRYRAHKSFLVIDNVMTEDAGDYTCCKFIHNENGANY
 SVTATRSFTVKDEQGFSLFVIGAPAQNEIKEVEIGKNANLTCSACFGKGTQFLAAVLWQLNGTK
 ITDFGEPRIQQEEGQNQSFSNGLACLDMLVRIADVKEEDLLQYDCLALNLHGLRRHTVRLSRK
 NPIDHHSIYCIIAVCSVFLMLNLVILKMFWEATLLWRDIAKPYKTRNDGKLYDAYVVYPRN
 YKSSTDGASRVEHFVHQILPDVLENKCGYTLCIYGRDMLPGEDVVTAVETNIRKSRRHIFILTPQI
 THNKEFAYEQEVALHICALIQNDAKVILIEMEALSELDMLQAEALQDSLQHLMKVQGTIKWRED
 HIANKRSLNSKFWKHVRYQMPVPSKIPRKASSLTPLAAQKQ

IL1RL1 amino acid sequence 2 (SEQ ID NO: 41)

NP_003847 interleukin 1 receptor-like 1 isoform 2 precursor; interleukin 1 receptor-related protein; homolog of mouse growth stimulation-expressed gene ; ST2 protein [Homo sapiens]

MGFWILAILTILMYSTAAKFSKQSWGLENEALIVRCPRQGKPSYTVDWYYSQTNKSIPT
 QERNRVFASGQLLKFLPAAVADSGIYTCIVRSPTFNRTGYANVTIYKKQSDCNVPDYL
 YSTVSGSEKNSKIYCPTIDLYNWTAPLEWFKNCQALQGSRYRAHKSFLVIDNVMTE
 GDYTCCKFIHNENGANYSVTATRSFTVKDEQGFSLFVIGAPAQNEIKEVEIGKNANLTCS
 ACFGKGTQFLAAVLWQLNGTKITDFGEPRIQQEEGQNQSFSNGLACLDMLVRIADVKE
 EDLLQYDCLALNLHGLRRHTVRLSRKNPSKECF

IL1RL1 amino acid sequence 3 (SEQ ID NO: 42)

NP_775661 interleukin 1 receptor-like 1 isoform 3 precursor; interleukin 1 receptor-related protein; homolog of mouse growth stimulation-expressed gene ; ST2 protein [Homo sapiens]

MGFWILAILTILMYSTAAKFSKQSWGLENEA LIVRCPRQGKPSYTVDWYYSQTNKSIPTQERNR
VFASGQLLKFLPAAVADSGIYTCIVRSPTFNRTGYANVTIYKKQSDCNVPDYLMYSTVSGSEKN
KIYCPTIDLYNWTAPLEWFKNCQALQGSRYRAHKSFLVIDNVMTEADAGDYTKFIHNENGANY
SVTATRSFTVKVWCQSFCKLKKSLIFSNTHWIQSLMRGFVMVYYGVHKCCRNVFNLCLQYFQH
HQWP

WASPIP amino acid sequence (SEQ ID NO: 43)

NP_003378 WASP-interacting protein [Homo sapiens]

MPVPPPPAPPPPTFALANTEKPTLNKTEQAGRNALLSDISKGKKLKKTVTNDRSAPILDKPKGA
GAGGGGGGFGGGGGGFGGGGGGGGGGSGFGGGGPPGLGGLFQAGMPKLRSTANRDNDSSGSRP
LLPPGGRSTSAKPFSPSPGPRFPVPSPGHRS GPPEPQRNRMPPPRPDVGSKPDSIPPPVPSTPRPIQ
SSPHNRGSPPVPGGPRQSPGPTPPFPGNRG TALGGGSIRQSPLSSSSPFSNRPLPPTPSRALDDK
PPPPPPVGNRPSIHREAVPPPPQNNKPPVPS TPRPSASSQAPPPPPPSRPGPPPLPSSSSGNDETP
RLPQRNLSLSSSTPPLPSPGRSGPLPPPPSERPPPPVRDPPGRSGPLPPPPVSRNGSTSRALPATPQL
PSRSGVDSRSGRPPPLPPDRPSAGAPPPPPPS TSIRNGFQDSPCEDEWESRFYFHPISDLPPPEPYV
QTTKSYPSKLARNESRSGSNRRERGA PPLPIPR

ADAMTS2 amino acid sequence 1 (SEQ ID NO: 44)

NP_055059 a disintegrin and metalloprotease with thrombospondin motifs-2 isoform 1; procollagen I N-proteinase;
Procollagen N-endopeptidase [Homo sapiens]

MDPPAGAARRLLCPALLLLLLLLLPPPLLPPPPPPANARLAAAADPPGGPLGHGAERILAVPVRTD
AQGRLVSHVVSAAATSRAGVRARRAAPVRTPSFPGGNEEEPGSHLFYNVTVFGRDLHLRLPNAR
LVAPGATMEWQGEKGTRVEPLLGSCLYVGDVAGLAEASSVALSNCDGLAGLIRMEEEFFIEP
LEKGLAAQEAQGRVHVYRRPPTSPPLGGPQALDTGASLDSLDSLSRALGVLEEHSRRRA
RRHAADDDYNIEVLLGVDDSVVQFHGKEHVQKYLLTLMNIVNEIYHDESLGAHINVVLVRILL
SYGKSMSLIEIGNPSQSLNVCWAYLQQKPD TGHD EYHDHAI FLTRQDFGPSGMQGYAPVTG
MCHPVR SCTLNHEDGFSSAFVVAHETGHVLGMEHDGQGNRCGDEVRLGSIMAPLVQAAFHFRF
HWSRCSQQELSRYLHSYDCLDDPFAHDWPALPQLPGLHYSMNEQCRFDFGLGYMMCTAFRTF
DPCCKQLWCSHPDNPFYCKTKKGPPLDGTMCAPGKHCFKGHCWLTDPILKRDGSGWAWSPFGS
CSRTC GTGVKFRTRQCDNPHPANGGRTCSGLAYDFQLCSRQDCPDSLADFREEQCRQWDLYFE
HGDAQHHWLPHEHRDAKERCHLYCESRETGEVVSMKRMVHDGTRCSYKDAFSLCVRGDCRK
VGCDGVIGSSKQEDKCGVCGGDNSHCKVVKGTFTSRPKKHGYIKMFEIPAGARHLLIQEVDATS
HHLAVKNLETGKFILNEENDVDASSKTFIAMGVEWEYRDEDGRETLQTMGPLHGTITVLVIPVG
DTRVSLTYKYMIEDSLNVDNNVLEEDSVVYEWALKKWSPCSKPCGGGSQFTKYGCRRLD
HKMVHRGFCAALSKPKAIRACNPQECSPVWVTGEWEPCSQT CGRTGMQVRSVRCIQPLHDN
TTRSVHAKHCNDARPESRRACSRRLCPGRWRAGPWSQCSVTCGNGTQERPVP CRTADDSFGIC
QEERPETARTCRLGPCRNISDPSKKS YVVQWLSRPDPDSPIRKISSKGHCQGDKSIFCRMEVLSR
YCSIPGYNKLSCSKCNLYNNLTNVEGRIEPPPGKHNDIDVFMPTLPVPTVAMEV RSPSTPLEVPL
NASSTNATEDHPETNAVDEPYKIHGLEDEVQPPNLIPRRSPYEKTRNQRIQELIDEMRKKEMLG
KF

ADAMTS2 amino acid sequence 2 (SEQ ID NO: 45)

NP_067610 a disintegrin and metalloprotease with thrombospondin motifs-2 isoform 2; procollagen I N-proteinase; Procollagen N-endorpeptidase [Homo sapiens]

MDPPAGAARRLLCPALLLLLLLLPPPLPPPPPPA~~N~~NARLAAAADPPGGPLGHGAERILAVPVRTD
 AQGRLVSHVVSAA~~T~~SRAGVRARRAAPV~~R~~TPSF~~P~~GGNEEEPGSHLFYNVTVFGRDLHLRLPNAR
 LVAPGATMEWQGEKGTTRVEPLLGSCLYVGDV~~A~~GLAEASSVALSNCDGLAGLIRMEEEFFIEP
 LEKGLAAQEA~~E~~QGRVHV~~V~~YRPP~~T~~SPPLGGPQA~~L~~DTGASLDSLSRALGVLEE~~H~~ANS~~S~~RRRA
 RRHAADDDYNIEVLLGVDDSVVQFHGKEHVQK~~Y~~LLTLMNIVNEIYHDES~~L~~GAHINVVLVRILL
 SYGKSMSLIEIGNPSQSLENVCRWAYLQKQPD~~T~~GHDEYHDHAI~~F~~LTRQDFGPSGMQGYAPVTG
 MCHPVR~~S~~CTLNHEDGFSSAFVVAHETGHVLGMEHDGQGNRCGDEVRLGSIMAPLVQAA~~F~~H~~R~~F
 HWSRCSQQELSRYLHSYDCLDDPFAHDWPALPQLPGLHYSMNEQCRFD~~F~~GLGYMMCTAFRTF
 DPCKQLWCSHPDN~~P~~YFCKTKKGPPLDGTMCAPGKFRPGAVAHACYPSTLGGQGRWIA

BVES amino acid sequence (SEQ ID NO: 46)

NP_009004 blood vessel epicardial substance; popeye protein 1; popeye domain containing 1 [Homo sapiens]

MNYTESSPLRESTAIGFTPELESIPVPSNKTTCEN~~W~~REIHHLVFH~~V~~ANICFAVGLVIPTTLHLHMIF
 LRGMLTLGCTLYVWATLYRCALDIMIWN~~S~~VFLGVN~~I~~LHLSYLLYKKRPVKIEKELSGMYRR~~L~~F
 EPLRVPPDLFRRLTGQFCMIQTLKKGQTYAAED~~K~~TSVDDRLSILLKGKMKVSYRGHFLHNITPC
 AFIDSPEFRSTQMHKGEKFQVTIADDNCRFLCWSRERLTYFLESEPF~~L~~YEIFRYLIGKDITNKLYS
 LNDPTLNDKKAKKLEHQLSLCTQISMLEM~~R~~NSIA~~S~~SSSDSDDGLHQFLRGTSMS~~S~~LHVSSPHQRA
 SAKMKPIEEGAEDDDVFE~~P~~ASPNTLK~~V~~HQLP

TM7SF3 amino acid sequence (SEQ ID NO: 47)

NP_057635 transmembrane 7 superfamily member 3; seven transmembrane protein TM7SF3 [Homo sapiens]

MGFLQLLVAVLASEHRVAGAAEVFGNSSEGLIEFSVGKFRYFELNRPFP~~E~~EAILHDISSNV~~T~~FLI
 FQIHSQYQNTTVSFSPTLLSNSSETGTASGLVFIL~~R~~PEQSTCTWYLGTSIQPVQ~~N~~MAILLSYSERD
 PVPGGCNLEFDLDIDPNIYLEYNFFETTIFAPAN~~L~~GYARGVDPPPCDAGTDQDSRWRLQYDVY
 QYFLPENDLTEEMLLKHLQRMVSVPQVKASALK~~V~~VTLTANDKTSVSFSSLPGQGV~~I~~YNVIVWDP
 FLNTSAAYIPAHTYACSF~~E~~AGEGSCASLGRVSSK~~V~~VFTL~~F~~FALLGFFICFFGHRFWKTELFFIGFIIM
 GFFFYILITRLTPIKYDVNLILTAVTGSVGGMFLVAVVW~~R~~FGILSICMLCVGLVLGFLISSVTFFTP
 LGNLKIFHDDGVFWVTFSCIAILIPVVF~~M~~GCLRILN~~I~~LTCGVIGSYSVVLAIDSYWSTLSYITLNV
 LKRALNKDFHRAFTNVPFQTND~~F~~IILAVWGMLA~~V~~SGITLQIR~~R~~ERGRPFPPHPYKLWKQERERR
 VTNILDPSYHIPPLRERLYGRLTQIKGLFQKEQPA~~G~~ERTPLLL

PELI2 amino acid sequence (SEQ ID NO: 48)

NP_067078 pellino 2 [Homo sapiens]

MFSPGQEEHCAPNKEPVKYGELVVLGYNGALPN~~G~~DRGRRKSRFALYKRPKANGVKPSTVHVIS
 TPQASKAISCKGQHSISYTL~~S~~RNQT~~V~~VVEYTHDK~~D~~DTDMFQVGRSTESPIDFVVTDTISGSQNTDE
 AQITQSTISR~~F~~ACRIVCDRNEPYTARIFAAGFDSSK~~N~~IFLGEKAAKWKNPDPGHMDGLTTNGVLV

MHPRGGFTEESQPGVWREISVCGDVYTLRETRS**A**QQRGKLVESETNVLQDGSLIDLCGATLLWR
TADGLFHTPTQKHIEALRQEINAAARPQCPVGLNT**L**AFPSINRKEVVEEKQPWAYLSCGHVHGYH
NWGHRSDTEANERECPMCRTVGPYVPLWLGCE**A**GFYVDAGPPTHAFTPCGHVCSEKSAKYWS
QIPLPHGTHAFHAACPFCA**T**QLVGEQNCIKLIFQGPID

LOXL1 amino acid sequence (SEQ ID NO: 49)

NP_005567 lysyl oxidase-like 1 [Homo sapiens]

MALARGSRQLGALVWGACLCVLVHGQQAQPG**Q**GSDDPARWRQLIQWENNGQVYSLNSGSEY
VPAGPQRSESSRVLLAGAPQAQQRSHGSPRR**R**QAPSLPLPGRVGSSTVRGQARHPFGFGQVP
DNWREVAVGSTGMALARTSVSQQRHGGSASS**V**SASAFASYRQQPSYPQQFPYPQAPFVSQY
ENYDPASRTYDQGFVYYRPAGGGVGAGAAVA SAGVIYPYQPRARYEEYGGGEELPEYPPQGF
YPAPERPYVPPPPPPDGLDRRYSHSLYSEGTPGF**E**QAYPDGPAAQAHGDPRLGWYPPYAN
PPPEAYGPPRALEPPYLPVRSSDTPPPGGERNGA**Q**QGRLSVGSVYRPNQNGRGLPDLVPDPNYV
QASTYVQRAHLYSLRCAAEKCLASTAYAPEAT**D**YDVRVLLRFPQRVKNQGTADFLPNRPRHT
WEWHSCHQHYHSMDEFSHYDLLDAATGKKVAEGHKASFCLEDSTCDFGNLKRYACTSHTQGL
SPGCYDTYNADIDCQWIDITDVQPGNYILKVHV**N**PKYIVLESDFTNVVRNCNIHYTGRYVSATN
CKIVQS

CASPR3 amino acid sequence 1 (SEQ ID NO: 50)

NP_207837 cell recognition protein CASPR4 isoform 1; **con**tactin associated protein-like 4 [Homo sapiens].

MLLFYLLVVLSDSTKASALTNPNVALFLLADDC**D**DPLVSALPQASFSSSELSSSHGPGFARLNR
RDGAGGWSPLVSNKYQWLQIDLGERMEVTAVA**T**QGGYGSSNWVTSYLLMFSDSGWNWKQYR
QEDSIWGFSGNANADSVVYYRLQPSIKARFLRFIP**L**EWNPKGGRIGMREVFGCAYRSEVVLDGK
SSLLYRFDQKSLSPIKDII**S**LKFKTMQSDGILLHRE**G**PNGDHITLQLRRARLFL**L**INSGEAKLPSTST
LVNLT**L**GSLLDDQHWHSVLIQRLGKQVNFTVDE**H**IRHHFHARGE**F**NLMNLDYEISFGGIPAPGKS
VSFPHRN**F**HGCLENLYNGVDIIDLAKQ**Q**KPQII**A**MGNVSFSCSQPSMPVTFLSSRSYLALPDFS
GEEEV**S**ATFQFRTWNKAGLLLFSELQLISGGILL**F**LSDGKLKSNLYQPGKLPSDITAGVELNDGQ
WHSVSLSAKKNHLSVAVDGQMASAAPLLGPEQ**I**YSGGTYFYGGCPDKSFGSKCKSPLGGFQGC
MRLISISGKVVDLISVQQGSLGNFSD**L**QIDSCGIS**D**RCLPNYCEHGGECSQSWSTFHCNCTNTGYR
GATCHNSIYEQ**S**CEAYKHRGNTSGFYIDSDGSG**P**LEPFLLYCNMTETA**W**TIIQHNGSDLTRVRN
TNPENPYAGFF**E**YVASMEQLQATINRAEHCE**Q**EF**T**YYCKKSRLVN**K**QDGTPLSWWVGRTNETQ
TYWGGSSPDLQKCTCGLEGNCID**S**QYYCNC**D**AD**R**NEWTNDTGLLAYKEHLPVTKIVITDTGRL
HSEAA**Y**KLGP**L**LCRGDRSF**W**NSASFDTEAS**Y**LHF**P**TFH**G**EL**S**ADV**S**FFFKTTASSGVFLENL**G**IA
DFIRIELRSPTVV**T**FSFDVGN**G**PF**E**ISVQSP**T**HFND**N**Q**W**HHVRVERN**M**KEASLQVDQLTPKTQPA
PADGHVLLQLNSQLFVGGTATRQ**R**GFLGCIRSLQ**L**NGMTLDLEERAQVTPEVQPGCRGHCS**S**YG
KLCRNGGKCRERPIGF**F**CDCTFSAYTG**P**FC**S**NEIS**A**YFGSGSSVIYN**F**QENYLLSKNSS**S**HAASFH
GDMKLSREMIKFSFRTTRTP**S**LLLFVSSFYKEYLS**V**IIAKNGSLQIRYKLNKYQEPDVVN**F**DFKN
MADGQLHHIMINREEGVV**F**IEDNRRRQVHLSS**G**TEFS**A**VKSLVLGRILEHSDVDQETALAG**A**Q
GFTGCLSAVQLSHVAPLKAALHP**S**HPDPVTVTG**H**VT**E**SSCMAQPGTDATSRER**T**HSFADHSGTI
DDREPLANA**I**KSDSAVIGGLIAVVIFILLCIT**A**IAVR**I**YQ**Q**KRLYKRSEAKRSENVDSAEAVLKSEL
NIQNAVNENQKEYFF

CASPR3 amino acid sequence 2 (SEQ ID NO: 51)

NP_620481 cell recognition protein CASPR4 isoform 2; **con**tactin associated protein-like 4 [Homo sapiens]

MWNYDCDDPLVSALPQASFSSSSELSSSHGPGFARLNRRDGA GGWSPLVSNKYQWLQIDLGER
 MEVTAVATQGGYGSSNWVTSYLLMFSDSGWNWKQYRQEDSIWGFSGNANADSVVYYRLQPSI
 KARFLRFIPLEWNPKGRIEMRIEVFGCA YRSEVVDLDGKSSLL YRFDQKSLSPIKDIIISLKFKTMQ
 SDGILLHREGPNGDHITLQLRRARLFLINSGEAKLPSTSTLVNLT LGSLDDQHWHSVLIQRLGK
 QVNFTVDEHRHHFHARGEFNLMNLDYEISFGGIPAPGKSVSFPHRNFGCLENLYNGVVDIIDL
 KQKQPQIIAMGNVSFSCSQPQSMPTVFLSSRSYLALPDFSGEEIEVSATFQRTWNKAGLLLFSEL
 QLISGGILLFLSDGKLKSNLYQPGKLPSDITAGVELNDGQWHS VLSAKKNHLSVAVDGQMASA
 APLLGPQIYSGGTYYFGGCPDKSFGSKCKSPLGGFQGCMLRISISGKVVDLISVQQGSLGNFSDL
 QIDSCGISDRCLPNYCEHGGECSQSWSTFHCNCTNTGYRGAT CHNSIYEQSCEAYKHRGNTSGF
 YYIDSDGSGPLEPFLLYCNMTETA WTIQHNGSDLTRVRNTNPNENPYAGFFEYVASMEQLQATIN
 RAEHCEQEFTYYCKKSRLVNKQDGTPLSWVVGRTNETQTYWGGSSPDQLKCTCGLEGNCIDSQ
 YYCNCDAADRNEW

GPR50 amino acid sequence 2 (SEQ ID NO: 52)

NP_004215 G protein-coupled receptor 50 [Homo sapiens].

MGPTLAVPTPYGCIGCKLPQPEYPPALIIIFMFCAMVITIVVDLI GNSMVILAVTKNKKLRNSGNIF
 VVSLSVADMLVAIYPYPLMLHAMSIGGWDLSQLQCQMVGFITGLSVVGSIFNIVAIAINRYCYIC
 HSLQYERIFSVRNTCIYL VITWIMTVLAVLPNMYIGTIEYDPR TYTCIFNYLNNPVFTVTIVCIHFV
 LPLLIVGFCYVRIWTKVLAARDPAGQNPNDQLAEVRNFLTMEFVIFLLFAVCWCPINVLTVLVAV
 SPKEMAGKIPNWLYLAAYFIA YFNSCLNAVYIGLLNENFRE YWTIFHAMRHPHIFFPGLISDIRE
 MQEARTLARARAHARDQAREQDRAHACPAVEETPMNVNRNVPLPGDAAAGHPDRASGHPKPHS
 RSSSAYRKSASTHHKSVFHSKAASGHLKPVSGHSPASGHPK SATVYPKPASVHFVKGDSVHFK
 GDSVHFKPDSVHFKPASSNP KPITGHHVSAGSHSKSAFSAATSHPKPIKPATSHAEPPTADYPKPA
 TTSHPKPAAADNPELSASHCPEIPAIAHPVSDSDLPESASSPA AGPTKPAASQLES DTIADLPDPT
 VVTTSTNDYHDVVVDVEDDPDEMAV

APOL3 amino acid sequence 2 (SEQ ID NO: 53)

NP_663615 Homo sapiens apolipoprotein L, 3 (APOL3), isoform 1, protein

MGLGQGWGWEASCFACLIRSCCQVVTFTFPFGFQGISQSLENVSGYYADARLEVGSTQLRTAGS
 CSHSFKRSFLEKKRFTEEATKYFRERVSPVHLQILLTNNEAWKRFVTA AELPRDEADALYEALK
 KLRTYAAIEDEYVQQKDEQFREWFLKEFPQVKRKIQESIEKL RALANGIEEVHRGCTISNVVSSST
 GAASGIMSLAGLV LAPFTAGTSLALTAAGVGLGAASAVTGITTSIVEHSYTSSAEAEASRLTATSI
 DRLKVFKEVMRDITPNLLSLLNNYYEATQTIGSEIRAIRQARA RARLPVTTWRISAGSGGQAERTI
 AGTTRAVSRGARILSATTSGIFLALDVVNLVYESKHLHEGAK SASAEELRRQAQELENLMELT
 QIYQRLNPCHTH

APOL3 amino acid sequence 2 (SEQ ID NO: 54)

NP_055164 Homo sapiens apolipoprotein L, 3 (APOL3), isoform 2, protein

MDSEKKRFTEEATKYFRERVSPVHLQILLTNNEAWKRFVTA AELPRDEADALYEALKKLRTYA
 AIEDEYVQQKDEQFREWFLKEFPQVKRKIQESIEKL RALANGIEEVHRGCTISNVVSSSTGAASGI

MSLAGLVLPFTAGTSLALTAAGVGLGAASAVTGITTSIVEHSYTSSAEAEASRLTATSIDRLKVF
 KEVMRDITPNLLSLLNNYYEATQTIGSEIRAIRQARARARLPVTTWRISAGSGGQAERTIAGTTRA
 VSRGARILSATTSGIFLALDVVNLVYESKHLHEGAKSASAEELRRQAQEELENLMELTQIYQRLN
 PCHTH

APOL3 amino acid sequence 2 (SEQ ID NO: 55)

NP_663616 Homo sapiens apolipoprotein L, 3 (APOL3), isoform 3, protein

MSLAGLVLPFTAGTSLALTAAGVGLGAASAVTGITTSIVEHSYTSSAEAEASRLTATSIDRLKVF
 KEVMRDITPNLLSLLNNYYEATQTIGSEIRAIRQARARARLPVTTWRISAGSGGQAERTIAGTTRA
 VSRGARILSATTSGIFLALDVVNLVYESKHLHEGAKSASAEELRRQAQEELENLMELTQIYQRLN
 PCHTH

[0348] Modifications may be made to the foregoing without departing from the basic aspects of the invention. Although the invention has been described in substantial detail with reference to one or more specific embodiments, those of skill in the art will recognize that changes may be made to the embodiments specifically disclosed in this application, yet these modifications and improvements are within the scope and spirit of the invention, as set forth in the aspects which follow. All publications or patent documents cited in this specification are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference.

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